MS 08-382
Special Issue on Pharmaceuticals in the Environment, 28:12

Running Head: Secondary routes for human and ecological exposure to drugs

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Word count

Text: 15,445

References: 4,459

Tables: 4,215

Environmental Footprint of Pharmaceuticals: The Significance of Factors beyond Direct Excretion to Sewers

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(Received 21 August 2008; Accepted 29 January 2009)

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Abstract–The combined excretion of active pharmaceutical ingredients (APIs) via urine and feces is considered the primary route by which APIs from human pharmaceuticals enter the environment. Disposal of unwanted, leftover medications by flushing into sewers has been considered a secondary route – one that does not contribute substantially to overall environmental loadings. The present study presents the first comprehensive examination of secondary routes of API release to the environment and for direct but unintentional human exposure. These include: bathing, washing, and laundering, all of which release APIs remaining on skin from use of high-content dermal applications or from excretion to skin via sweating, and disposal of unused and partially used high-content devices. Also discussed are the health hazards associated with: partially used devices, medication disposal practices of consumers, and interpersonal dermal transfer of API residues. Understanding these secondary routes is important from the perspective of pollution prevention, as actions can be designed more easily for reducing the environmental impact of APIs compared with the route of direct excretion (via urine and feces), as well as for reducing the incidence of unintentional and purposeful poisonings of humans and pets and for improving the quality and cost-effectiveness of healthcare. Overall, unintentional exposure to APIs for humans via these routes is possibly more important than exposure to trace residues recycled from the environment in drinking water or foods.

Keywords–Pharmaceuticals; Excretion; Sweat; Poisoning; Disposal

Introduction

Pharmaceuticals and personal care products (PPCPs) as environmental pollutants is a subject that has received exponentially growing attention since the late 1990s. The U.S. Environmental Protection Agency (U.S. EPA) maintains a large, publically available literature citation database for PPCPs ([1] http://www.epa.gov/ppcp/lit.html). It currently catalogs over 6,000 citations covering aspects that are directly or peripherally related to the entire spectrum of the risk paradigm – from origin and sources, to fate and transport, source control and waste treatment, ecological and human exposure, biological effects, pollution prevention, risk management, risk perception/communication, modeling, and others. Among these thousands of publications, however, fewer than 200 address any of the aspects of leftover (expired or unwanted) drugs and their disposal. None discuss the secondary routes by which active pharmaceutical ingredients (APIs) enter the environment (those beyond direct excretion to sewers) or that serve as source terms for modeling human exposure. The present study is the first comprehensive examination of the hazards of drug disposal and the potential significance of the secondary routes by which APIs enter the environment. This includes summarizing what the published literature covers as well as highlighting the data gaps and needs, and a framework, termed pharmEcokinetics (PEK), as the umbrella under which these processes and their relative significance might be better understood.

Widespread occurrence of APIs in the environment is now well-established. Published reports of the occurrence of APIs in sewage, surface and groundwaters, sediments, sewage sludge, biota, and elsewhere in the environment total over 1,000 as of August 2008 ([1], http://www.epa.gov/ppcp/lit.html); many of these studies were catalyzed after the seminal 2002

92 publication of the initial nationwide monitoring study by the U.S. Geological Survey (USGS)
93 [2].

94 The environmental presence of APIs is attributed primarily to raw or treated sewage (for
95 human drugs) and to manure and lagoons (for veterinary drugs used in animal feeding
96 operations); additional, less-obvious sources also exist, which can sometimes play important
97 localized roles [3]. The major route by which APIs enter sewage is commonly accepted to be via
98 urine and feces, with each contributing different relative amounts depending on the
99 pharmacokinetics and structure of the individual API [4]. While other contributory routes, such
100 as personal hygiene bathing or washing and the disposal of leftover medications by consumers,
101 have been considered minor or inconsequential [5-7], no empirical evidence has yet been
102 published to support this supposition.

103 Specifically with respect to the disposal route, prior work regarding leftover, unwanted
104 medications has covered the following aspects: the broad spectrum of locales in society where
105 unused drugs accumulate and from where they must be disposed or stockpiled [3, 8]; the many
106 factors that lead to the accumulation of leftover medications, which then in turn eventually result
107 in the need for their disposal [8]; the many approaches having the potential to minimize or
108 reduce the accumulation of unused, leftover drugs and therefore reduce the need for disposal [8-
109 10]; disposal of consumer drugs via collection programs in the U.S. [11]; the factors that
110 encourage disposal to sewers versus other means of disposal such as trash or formal means of
111 collection (e.g., take-back events) [12-14]; the first methodology by which accurate and
112 comprehensive empirical data on the actual types and quantities of individual APIs that are
113 disposed can be collected for a particular, defined population - namely coroner records from

114 decedent investigations [15]; and the human health, medical, and environmental ramifications
115 and consequences of accumulated, leftover drugs [16, 17].

116 As for bathing or washing as a route of release and the hazards of leftover medications and
117 the disposal process, no formal discussion has ever been presented to our knowledge, other than
118 brief mentions ([3]).

119 In the present study, disposal is placed into a formal context for assessing its significance.
120 The potential significance of washing and dermal transfer to other surfaces as contributory routes
121 is also examined. Disposal and washing/bathing are discussed as the two most important
122 secondary alternate routes of API release to the environment. The context required to assess their
123 relative significance as contributory routes is developed. Understanding these routes is important
124 from the perspective of pollution prevention, as actions can then be designed more easily for
125 reducing their environmental impact compared with the route of direct excretion (via urine and
126 feces), as well as for reducing the incidence of unintentional and purposeful poisonings of
127 humans and pets. It is worth noting that while the literature on the larger topic of PPCPs as
128 pollutants has grown dramatically since the mid-1990s [1], the total number of publications
129 (beginning in the late 1980s) that tackle the questions surrounding disposal from a scientific
130 perspective are few. This means that the single aspect of the problem involving environmental
131 and human exposure having the greatest potential for control (i.e., disposal) has received the
132 least attention. This bias has arisen perhaps because disposal has generally been assumed to
133 contribute little to environmental residues compared with excretion.

134 Also introduced here is the concept of PEK. In simple terms, conventional
135 pharmacokinetics (PK) deals with how a drug is processed in an organism (mainly, the time-
136 course of drug concentration), with the prime focus being on the eventual concentration that

becomes bioavailable, so that therapeutic effect can be optimized and side-effects minimized: "The activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, [transformed], and excreted" ([18], http://www.cancer.gov/templates/db_alpha.aspx?CdrID=44324). Since PK focuses on the active (plasma) concentrations of drugs, excretion is only of indirect interest to pharmacologists (sometimes measured solely for mass balance and to get a better idea of the portion of API that might still be available within the body and to calculate half-lives). PharmEcokinetics is analogous to PK by also considering the fate of APIs in the environment (beginning at the point where an API or metabolite is excreted), with the primary difference being that its focus is decidedly not on plasma levels, but rather environmental levels, particularly wastewater, drinking water, and biosolids, as well as other locations (e.g., biota). The major aspects of PK that are of interest for PEK in environmental modeling are all of the pathways of excretion of unchanged parent API (and bioactive metabolites and labile conjugates).

To date, the routes of excretion that are factored into environmental modeling are urinary and fecal, both having been long assumed to be the major contributors to ambient environmental residues. While these generalizations are probably correct for APIs overall, the possibility has not been ruled out that they might not apply to certain APIs. While direct disposal of unused APIs is recognized as an additional source for entry to the environment, its significance is unknown and generally deemed to be inconsequential. Another route, which has essentially been ignored is release of API residues from the skin, by bathing and washing (including laundering of clothing and bedding contaminated by dermal contact) and by direct transfer via surface contact.

Disposal has two distinct contributors: leftover unused medications (i.e., expired, unwanted, or unused for other reasons), and partially used medications that retain residual API (delivery devices such as transdermal or transmucosal delivery systems). Approaches to pollution prevention could differ for these two sources. Washing, bathing, and dermal transfer by direct contact have three contributors: residues remaining after the administration of dermal medications - APIs for local treatment (topical use) and systemic treatment (transdermal/transmucosal delivery), residues remaining on the skin after removal of transdermal systems (e.g., patches), and residues excreted via sweat, a route that has only been briefly discussed with respect to its possible role in environmental pollution [16, 19].

Historically, consumers and other end users in the United States (U.S.) have disposed of leftover, unwanted medications by flushing them down sewer drains or by discarding them in the trash. For the vast majority of medications, the most prudent approach for addressing leftover medications is to avoid disposal to sewers. A number of countries (but not the U.S.) have long had programs where consumers can return leftover medications to pharmacies). In the last few years, various cities in the U.S. have begun implementing take-back collection programs, where consumers can return their unwanted medications [11]; in the U.S., however, these types of collection programs can be complicated by the presence of controlled substances, which can only be transferred by the prescription holder to law enforcement (and their deputies) or agents of the Drug Enforcement Administration (DEA), or among DEA registrants [3].

Drug diversion (the use of licit drugs for purposes that differ from their original purpose; recreational use is one example) is an important public health and safety concern and occurs by various routes, such as burglaries of residences and pharmacies, breaches of the manufacturing, distribution, prescribing, and dispensing chains, and theft by family and friends (e.g., teen

pharming) [20]. For medications that pose extraordinary and imminent hazards to humans (e.g., those subject to abuse or those having high acute toxicity), the possibility of unintentional poisonings or diversion for abuse must be minimized, as medications are a major cause of poisonings in the U.S. The United States Poison Control Centers recorded over 1,330,000 cases of unintentional non-fatal poisonings by chemicals in 2003, 42.6% involving children aged 5 and younger. During 2001 to 2003, the United States Centers for Disease Control estimated over 53,000 children aged 4 and younger (72% of which were aged 1-2) suffered unintentional poisoning from OTC (over-the-counter) and prescription medications [21]. Nearly 10% required special medical care. Over 75% occurred in homes. A survey of death certificate data indicates a considerable presence of drug-related mortality, specifically overdoses [22].

Imprudent storage and disposal (e.g., to trash) is possibly a major cause of unintended exposures of those for whom the medication was not prescribed or intended, especially children [21]. Trade-offs are therefore required to best balance exposure of the environment (primarily via disposal to sewers) versus human exposure (e.g., via diversion from stored stockpiles of leftovers or from those medications disposed into the trash). It is widely accepted that a select number of medications are still best disposed by flushing to sewers as soon as they are no longer needed. This limited list of medications includes those that remain unused as well as certain ones (such as transdermal patches) that retain appreciable residuals after being completely or partially used. A list of these medications is highlighted by the White House Office of the National Drug Control Policy as part of their drug disposal guidance for consumers ([23], http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf). This guidance, however, is in a state of flux and is subject to modification, especially because of the intricacies presented by the Controlled Substances Act ([24],

205 http://www.deadiversion.usdoj.gov/fed_regs/rules/2009/fr0121.htm). Note that unanticipated
206 adverse ecological consequences have also occurred from the veterinary use of drugs that have
207 resulted in drug-contaminated waste; two noteworthy examples are pentobarbital and diclofenac,
208 which have resulted in considerable adverse impacts on populations of raptors and vultures [3].

209 A major unanswered question, however, is what portions of environmental residues of APIs
210 originate as a result of intended therapeutic use, disposal, and washing/bathing. The approach
211 presented here is intended for assessing the significance of these alternate pathways. The API
212 contributions from these pathways is important in order to gage the possible efficacy of pollution
213 prevention efforts for reducing environmental loads and to assess the hazard for humans.
214 Evidence already exists that reducing the accumulation of drug waste has benefits with respect to
215 healthcare, for which waste reduction is particularly attractive as a strategy because it imposes no
216 limits on the overall usage of medications, it does not adversely affect the quality of healthcare
217 [17], and may even serve to improve it [16].

218 In calculating predicted environmental concentrations, a variety of assumptions are required
219 for the many inputs for a model's variables [25 - 27]. Three factors for which practically no
220 empirical data are available are: the portions of medications that are disposed to sewers; the
221 portions of APIs discharged to sewers resulting from the use of medications designed for dermal
222 use; and the contributions from oral/parenteral formulations that are washed from the skin – as a
223 result of excretion from eccrine and apocrine sweat.

224 With respect to disposal, the extensive examination of predicted environmental
225 concentration calculations performed by Kostich and Lazorchak [25] had to assume that the
226 following portions of medications are disposed to sewers: medicines prescribed for short-term
227 therapy (15%), for long-term therapy (5%), and topical medicines (33%). Unfortunately, there

228 are no empirical data to validate these assumptions. These generalizations are likely much too
229 high or too low when applied to many specific APIs.

230 Also with respect to disposal, another factor must be evaluated for delivery devices,
231 especially transdermal systems, as the API residuals in used, high-content devices can be
232 substantial (over 50% of the original API can remain); with patches, whose initial API content
233 can exceed by 20 fold that which is eventually absorbed, more than 95% of the initial API
234 content can remain in the used patch [28]. This means that for used patches, which are
235 commonly disposed by flushing, the majority of the API from the used medication can be
236 eventually disposed via sewers. Also, while the portion of API excreted via urine and feces is
237 considered (as a major contributor), no consideration is given to the portion of unchanged API
238 that might be excreted via sweat (because such data are extremely rare for prescription and OTC
239 drugs) or the portion remaining on the skin after dermal application. Finally, the need to assume
240 single, average values for individual factors for all APIs in general does not accommodate for the
241 extreme ranges that actually exist among individual APIs.

242 Once a prescription drug is dispensed to an end user or an OTC medication is purchased,
243 there are at least seven factors that have received little attention in previous modeling efforts and
244 which determine whether disposal or bathing become important factors with respect to the
245 overall occurrence of APIs in the aquatic environment (**Table 1**). **Figure 1** summarizes these
246 factors and shows their interconnections.

247 In determining the significance of these secondary routes by which APIs can enter the
248 environment, several key questions are prompted. For APIs with a presence in ambient waters,
249 what individual portions or individual APIs originate from direct disposal of leftover, unwanted
250 medications; release by bathing of residues remaining on the skin from dermally applied

medications; and release by bathing of residues remaining on the skin from excretion via sweat? Another source, related to the last two factors, is laundering, as drugs present on the skin can be transferred to clothing and bedding. Note that the release of topically applied drugs from domestic animals is also a source of APIs in the environment [29].

From these data, rankings could eventually be prepared to show which drugs contribute the most and least mass of APIs to the environment via disposal and via washing, in terms of absolute amounts as well as relative to the amounts contributed directly via excretion. This would allow the development and better targeting of pollution prevention measures and better targeted environmental monitoring.

Regardless of what percentage of APIs in the environment might be contributed to sewers by disposal or bathing, these practices could lead to transient, episodic spikes in API concentrations. These momentary concentrations could be orders of magnitude greater than what are being continually introduced via direct excretion [16]. Note, however, that those APIs for which disposal and bathing contribute the largest portion of their presence in ambient waters, this still would not reveal the relative importance of disposal or bathing with respect to the potential for actual adverse impact to the environment.

For a given API, the total mass discharged to sewers as a result of disposal and washing/bathing (WM) could be calculated from the factors in Table 1 according to:

$$WM = UR(mass) \bullet [(DP \bullet PDs) + (SMP + RD + TD)] \qquad (1)$$

The relative significance (Sr) of the contribution from these alternate routes (versus direct excretion) for a particular API could be calculated by dividing the total mass contributed by disposal and washing/bathing by the total mass excreted unchanged in urine and feces:

$$Sr = WM \bullet [(UR - WM) \bullet PMP]^{-1} \qquad (2)$$

where UR is the usage rate; DP this is disposal potential (portion of API leftover); PDs are the method of disposal (portion disposed to sewers); PMP is the primary metabolic profile (portion excreted in urine/feces); SMP is the secondary metabolic profile (portion excreted by other routes such as sweat); RD is the route of delivery(portion remaining on skin after dermal application); and TD is the type of delivery system or container (portion of dose remaining in device).

As the portion of an API in sewage resulting from the alternative disposal routes increases (as WM increases, or as the portion used-as-intended decreases), Sr increases. As the portion resulting from disposal decreases, Sr approaches zero. In the absence of values for UR, however, Sr cannot be fully evaluated.

One factor regarding the correlation of disposal with intended usage needs to be emphasized, as it would complicate STET efforts at modeling. Sales are not linked in time to disposal. Disposal always occurs from sales made in the past. This time lag can also vary, forcing gross simplifications for the purposes of modeling. The significance of the time lag between dispensing and when leftovers will be disposed diminishes as the time period examined increases. In other words, the correlation over time between sales figures and if/when the drug is disposed will improve as the time period examined increases (perhaps extending out to the shelf-life of the drug). The consistency of correlation between sales and disposal over time is a function of the consistency in sales. For a medication whose usage (as reflected by sales) remains constant over time, the rate of disposal during a given time period will probably best correlate with the sales during that same time period even though the disposal results from sales during a prior time period. With this complication in mind, special circumstances become evident when

disposal could become the primary source of an API in the environment. For example, the environmental contributions from disposal might be greater than from intended usage if the sales for a medication dropped precipitously, for example, if the drug lost market share quickly or if it was recalled by the United States Food and Drug Administration. Likewise, the relative contributions from disposal would be less should a medication experience a rapid increase in sales, removed for example, an antiviral/antimicrobial drug dispensed during epidemics.

Clearly, to model the contributory origins of APIs present in the environment requires far more empirical data than currently exists. The empirical data necessary for many of the factors in Table 1 are not available. What is currently known regarding these previously unexplored factors is discussed in the remainder of the present study.

Sweat as a route of excretion

While most unmetabolized, parent APIs are excreted via feces and urine, often overlooked is that measurable quantities of many APIs and/or their metabolites can be excreted via sweat. Excretion via sweat has been known at least since the 1950s, with one of the very early studies being published by Thaysen and Schwartz [30]. While the initial studies (up until the 1990s) focused on therapeutic drugs, interest has since shifted to illicit drugs, where sweat has become a matrix for monitoring illicit drug usage. Most of this literature therefore deals with what is known as sweat-patch testing as a means of non-invasive monitoring; see overviews by Rouen et al, ([31], http://notes.med.unsw.edu.au/ndarcweb.nsf/resources/TR_18/$file/TR.120.PDF) and Fortner [32]. Upon oral ingestion (or any other means of drug delivery), excretion of the original dose via sweat can continue for anywhere from a day to weeks. Excretion can begin in less than an hour, and varies from drug to drug. Excreted residues can then be collected on absorbent patches affixed to the skin. The concentration in sweat might vary depending on the sweating

rate, with the rate for some APIs remaining the same and others increasing with increasing rate of sweating [33].

Sweat contributes to two pathways for transporting APIs to the immediate and surrounding environments: direct exposure of others and contamination of surrounding objects via dermal contact (e.g., drugs released in sweat through the rows of pores located along fingerprint ridges are known to be deposited in fingerprints) [34], and release of APIs directly to sewers, via bathing and other hygiene activities.

Insensible sweat (passive diffusion through the skin) is produced at a rate of 300 to 700 ml/d per individual (at a rate of up to 100 $g/m^2/h$ in air temperatures below 31 °C). With rigorous exercise, sensible sweat production (primarily from eccrine glands and secondarily from apocrine glands) can increase to 2 to 4 L/h for short periods or 1 L/h for prolonged periods. Eccrine sweat glands are distributed widely across the body, whereas the apocrine glands have very limited distribution; apocrine glands excrete via the hair follicles. As the largest organ of the body (and comprising 10% of body mass), the average skin surface area is very roughly 2 m^2 [35]. Drugs become incorporated with sweat via passive diffusion through cellular membranes driven by the concentration gradient established by the free drug in plasma and fat depots. Since sweat is normally very slightly acidic (pH <6.5) and blood is slightly alkaline, those drugs that are primarily non-ionized in plasma experience a negative concentration gradient across the skin (because they become ionized in the accumulating sweat). Therefore, excretion and accumulation in sweat favors those APIs that are neutral at around pH 7.4. See overviews by Tobin [36] and Fortner [32]. Excretion via sweat also seems to discriminate against polar metabolites. One extreme example is cocaine, which is extensively excreted in urine as ecgonine

methyl ester and its hydrolytic product, benzoylecgonine. But in sweat, cocaine is extensively excreted in its unchanged parent form [37].

While the concentrations of APIs in the aqueous natural environment are generally very low [7, 38], usually less than 1 μg/L, it is not known what the relative contributions might be among urine/fecal excretion, disposal, or bathing. The extent and magnitude of excretion via sweat, and its significance with respect to contributing APIs to sewage, is clearly largely dependent on the amount (and type) of sweat that is generated per day (which can vary widely depending on the individual, the level of activity, level of hydration, the temperature/humidity, level of stress, the content and distribution across the skin surface of apocrine and eccrine sweat glands, and health and skin condition of the individual), the pH of the sweat, the plasma concentration and pK_a of the API, and the bathing frequency, among other factors.

Despite the use of sweat-patch testing for illicit drugs, the published quantitative data on excretion of commercial drugs via sweat is rather limited. Most of the major studies are summarized in **Table 2**; note that in this discussion, sweat from eccrine and apocrine sources is not distinguished. The data on excretion via sweat is generally not obtained for the PK studies performed on a drug for registration purposes. Instead, these data are obtained during independent research studies. The excretion data provided by PK studies could perhaps be used, however, as an indirect indicator of the possible extent of excretion via sweat (e.g., by examining mass balance discrepancies of the percentage of an API not accounted for by excretion via urine and feces); but these studies are generally done under comfortable conditions where excretion via sweating would be minimized. If the excreted API is continually removed (e.g., via bathing or periodic re-contact with clothing), then the amount reabsorbed would be minimized. Also note that only recently has it become possible to accurately determine the actual concentration of

xenobiotics in sweat as determined with sweat-patch testing. Appenzeller et al. [39] normalized the quantities collected on patches to the content of sodium ion. Without normalization, excretion rates can only be roughly estimated by making assumptions regarding sweat volume production rate and collection efficiency.

Significance of excretion via sweat as a contributor to environmental residues

By performing some rough calculations, a general estimate of the relative contribution of APIs from sweat versus fecal/urine excretion can be obtained. The total amount of many APIs excreted via sweat may comprise very roughly up to 2 % of the total oral (or parenteral) dose. For those APIs that are the most extensively metabolized (e.g., when the percentage of parent API excreted unchanged and not in conjugated forms is less than a 2%), the contribution from sweat could prove to be an important factor.

The following serve as examples. Using the ratio of the areas of the sweat patch and body surface area, Pichini et al. [35] derived a crude estimate of the total amount of 3,4-methylenedioxymethamphetamine excreted via sweat 24 h after a 100-mg oral dose. The mean total mass excreted via sweat was estimated as 0.6 mg with an upper range of 1.5 mg (because of large inter-individual variability). This amounts to at least 0.6% (and 1.5%) of the total excreted (assuming methylenedioxymethamphetamine is extensively excreted unchanged).

After daily doses of 1,500 mg of ciprofloxacin, assuming a conservative rate of sweat production of 1 L/d, and assuming sweat concentrations ranging from 2 to 23 μg/ml [40], the total daily excretion of ciprofloxacin in sweat would range from 2 mg/d (2 μg/ml • 1000 ml/d) to 23 mg/d. Assuming that ciprofloxacin is extensively excreted unchanged, the fraction excreted via sweat would be roughly 0.1 to 1.5% of the total available.

For drugs that are extensively excreted unchanged, the portions contributed by sweat are measurable but, as seen from these examples, not very significant (e.g., roughly less than 2%). For these drugs, the importance of excretion via sweat would more likely be dispersion to the immediate environment via dermal contact. For drugs that are extensively metabolized, however, the contribution to excreted APIs via sweat could be considerable and should probably be considered in predictive fate models.

Consider another example applied to a drug (fentanyl) that is more extensively metabolized (less than 8% excreted unchanged in the urine). In this case, the majority of the dose that is excreted might be excreted via sweat rather than urine. Schneider et al. [41] calculated the amount of fentanyl excreted via sweat as ranging from 19 to 150 μg/d, which translates to 3 to 25% of the total daily dose (600 μg). Relative to the amount imputed to be excreted in the urine (8%), the relative amount contributed by sweat would have ranged from 40 to 300%. As for many drugs, measurable quantities are also excreted via the hair (through apocrine sweat), but this is harder to quantify on a per-body basis. So for a drug that is not extensively excreted in the urine or feces unchanged, the portion excreted via sweat could be comparatively significant.

Using the data of Schneider et al. [41], a series of calculations were made using a different approach. The minimum mass of fentanyl excreted per day via sweat could be calculated from the minimum amount found on a sweat patch (5.7 ng) and using 1.5 m^2 as the body skin surface area. The maximum mass of fentanyl excreted per day via sweat could be calculated from the maximum amount found on a patch (88 ng) and using 2.0 m^2 as the body skin surface area. Calculating the number of patches that could hypothetically cover the body (total area in mm^2 divided by 1480 mm^2/patch), and using the fraction of a day during which sweat was collected (0.42 d = 611 mins), the range of fentanyl mass excreted via sweat would have been 17 to 284

μg/d/body. Since the presumed daily dose was 600 μg, the percentage of the dose excreted via sweat could have ranged from 2.8 to 47%. It must be noted, however, that the heterogeneity of sweat excretion (as well as the concentrations of APIs in different microenvironments of sweat) could vary greatly. Therefore, all extrapolations on total amounts of API excreted are subject to considerable error. Insufficient data exist regarding API excretion to fully understand total-body excretion via sweat.

Assuming that only 8% of a fentanyl dose is excreted unchanged via urine each day (which in this example is 48 μg), the range in mass excreted via sweat would have been equivalent to that excreted from the following number of daily doses delivered via patch (in terms of relative contributions of fentanyl to sewage): 17/48 to 284/48 = 0.35 to 5.9. Of course, there are many variables, including actual skin area over which sweating occurs, uniformity of sweating over the body, uniformity of sweating rate (which could be seen as varying over a 15-fold range), uniformity of excretion via sweat, uniformity of rate of fentanyl absorption (which determines plasma concentration), etc. But from these crude calculations, the contribution of fentanyl to sewers via washing of sweat from the body could be equivalent to 30 to 600% of the mass originating from urine, in agreement with the estimates provided by Schneider et al. [41].

With respect to medications, appropriate exposure results from use by those for whom the API was intended and for whom the API was deemed safe, and inappropriate exposure occurs to those for whom the API was not intended (or for whom the API is contraindicated, or for whom the exposure was unwelcome). Inappropriate exposure to APIs via interpersonal dermal transfer (or hand-mouth contact) might prove to be a more important source of exposure than exposure via drinking water. A comparative yardstick might be that the occurrence of APIs in sweat can reach concentrations at least 3 orders of magnitude higher than those eventually occurring from

recycling of residues from the environment via drinking water. Drinking water concentrations are generally much less than 1 μg/L [42] versus concentrations in sweat, which are roughly 1 μg/ml and higher. The very limited numbers of oral/parenteral APIs that eventually make their way into finished drinking water [42] must survive a series of steps that successively reduce their concentrations, including absorption and metabolism, sewage treatment, dilution in receiving water, environmental transformation, sorption to sediments, and final polishing to produce finished drinking water. A broader spectrum of APIs at much higher concentrations could therefore occur in sweat, including those that are otherwise extensively metabolized.

While direct exposure to APIs via contact with the sweat of others has unknown significance, the APIs excreted from the skin of those taking medications (including those undergoing chemotherapy) have the potential to be fully released from the entire body in public spas and swimming pools. This is a scenario where inappropriate or unwanted dermal contact could occur to concentrations higher than in waters from the ambient environment (e.g., > 1 ppb, ng/L). For those undergoing polypharmacy, the release of multiple APIs would likely occur.

The use of recently developed ambient surface-sampling/direct desorption mass spectrometry techniques (such as DESI, DART, and DAPCI or single-particle aerosol mass spectrometry – SPAMS) for the very fast in vivo surface-analysis of tissues could prove very useful for the broad survey of the prevalence of APIs excreted to the surface of skin, as well as items commonly touched by the public. These techniques excel at rapid identification of chemicals sorbed to complex solid substrates. The abilities of these techniques to readily detect drugs and metabolites on skin have been demonstrated by Martin et al. [43], Takats et al. [44], and Williams et al. [45]. Application of this type of technique could be used to quickly reveal the

454 extent and magnitude of drug excretion via skin and the indirect contamination by APIs by
455 dermal transfer.

456 A final note is warranted regarding the significance of excretion via sweat. Much has been
457 published regarding the growing prevalence of antibiotic resistance, especially among human
458 pathogens. Excretion of antibiotics via sweat has been proposed as a possible major means of
459 quickly promoting and spreading resistance. The comparatively higher and sustained
460 concentrations on skin can serve to expose dermal bacteria, which can then be readily transferred
461 to other locations or people. This has been demonstrated by Høiby and others [40, 46], who
462 documented the excretion onto skin of floxacin and β-lactam antibiotics where bacteria would
463 come into ready contact. This could be an overlooked cause of transmission of multiresistance
464 among bacteria in hospitals and other care facilities that routinely administer antibiotics.

465

466 *Chemotherapeutics in sweat*

467 Excretion of chemotherapeutics via sweat is well established, but its overall significance as
468 a secondary exposure route for others is not. That chemotherapeutics are excreted via sweat is
469 reflected by its becoming recognized as a primary cause of a variety of adverse cutaneous effects
470 during chemotherapy (e.g., doxorubicin), including hand-foot syndrome (hand-foot skin
471 reaction) [47, 48] and hyperpigmentation and alterations to nails. The specific formulation can
472 enhance the excretion of the API via sweat.

473 But with respect to unanticipated exposure, this route of excretion holds the potential for
474 promoting subsequent incidental exposures for others and poses higher risks than for other drugs
475 because of the extreme cytotoxicity and mutagenicity of oncolytics. Excretion via sweat

undoubtedly also plays a role in the development of hypersensitivity to certain other drugs since it ensures skin contact with drugs not intended for dermal application.

Early studies indirectly measured the excretion of chemotherapeutics via sweat by mutagenicity assays. For example, a 1988 study showed that sweat collected from patients treated with cyclophosphamide and other antineoplastics showed greater mutagenicity than controls 8 h after treatment [49]. A mean concentration of methotrexate in sweat was measured as 725 ng/ml (mean maximal concentration of 1.7 μg/ml), calculated as translating into excretion of 300 μg per day through sweat [50]. Other studies provide strong indirect evidence that sweat conveys chemotherapeutics outside the body. These studies have focused on studies of occupational exposure [51], where bedding becomes contaminated and serves as a route of exposure for healthcare workers and especially those working outside hospitals, such as home care providers [52]; workers in laundry facilities were noted as having the potential for higher exposures to antineoplastics than oncology nurses during the handling of bed sheets.

Chemotherapeutics and pulmonary exposure

Occupational exposure to antineoplastic agents has been well documented, especially direct exposure from the compounding, preparation, administration, and disposal of these highly toxic chemicals. Of the many routes of exposure, however, the excretion of residues via sweat (and breathing) of patients has been less understood. Several chemotherapeutics have appreciable vapor pressures. These include: carmustine, cyclophosphamide, ifosfamide, thiotepa, and mustargen [53]. Others have much lower vapor pressures: doxorubicin, cisplatin, etoposide, 5-fluorouracil, and mitomycin. Kiffmeyer et al. [54] determined that the vapor pressures of five antineoplastics (carmustine, cisplatin, cyclophosphamide, etoposide and fluorouracil; and one

antimicrobial drug, fosfomycin) were all low but with carmustine having a vapor pressure one order of magnitude higher. Nevertheless, cyclophosphamide was still detected in the gas phase in 7 out of 15 locations, at levels ranging from 45 ng/m^3 to 13μg/m^3. Inhalation of excreted cytotoxics could also be enhanced for those who work in laundry facilities that clean bedding and clothes from patients [52], although Fransman et al. [55] did not detect vaporization of antineoplastics from bedding at a laundry facility.

These data also indicate the theoretical potential for pulmonary exposure to the expired breath from those undergoing treatment. Fransman ([56], http://igitur-archive.library.uu.nl/dissertations/2006-1003-200854/full.pdf#page=131) notes that exposure to people or animals associating with those undergoing treatment with antineoplastic drugs has not been investigated. Unintended exposure in these settings could prove important with the increasing usage of antineoplastics in outpatient and veterinary clinics and since more intimate and chronic interpersonal contact can occur in the household.

Dermal application

The continuing trend toward the dermal application of drugs will increase the probability of drugs being introduced to the environment as a result of: release via bathing of concentrated residues remaining on skin and discarding the used delivery device (e.g., patches) which often contains very high levels of residues (sometimes considerably greater amounts than would have been needed orally). It could also increase the unintended risk of exposure to others by direct dermal-dermal contact and transfer, and from indirect exposure via contact with contaminated objects.

521 A wide array of drugs are available in topical form ([57],
522 http://formulary.prescribingreference.com/dermatological_disorders; [58]). See **Table 3** for those
523 that are commonly employed. The concentrations of APIs in these topical preparations range
524 from a fraction of a percent to 5% and more, by weight. They include potent steroids, antibiotics,
525 pesticides (e.g., lindane, malathion), immunomodulators (e.g., pimecrolimus), a psychotropic
526 (doxepin), and cytotoxics (e.g., fluorouracil). Some of these drugs have no routine oral use
527 (because of toxicity or facile metabolism), such as tolnaftate, ciclopirox, flurandrenolide, and
528 imiquimod. For these drugs, bathing (and disposal) is most likely to account for the vast majority
529 of any residues that might be detected in the environment. For others that also have equivalent
530 oral uses, but are extensively metabolized (little excretion of unchanged API), bathing could still
531 be a major contributor of residues to sewage.
532 Those APIs with equivalent dermal and oral uses, but which are extensively excreted
533 unchanged, are highlighted in Table 3. This group comprises the only topical APIs where
534 washing and bathing could be competing with excretion from oral/parenteral use in terms of
535 contribution to the environment and therefore where bathing would be a less important source.
536 The APIs in this group (highlighted by footnotes in Table 3) are: acyclorvir, doxepin,
537 fluorouracil, metronidazole, neomycin, nystatin, polymyxin, sulfadiazine, tobramycin, and
538 tretinoin. All the remaining APIs in Table 3 (those not highlighted), if detected in the
539 environment, could have origins primarily from dermal application. These latter APIs could be
540 ranked according to overall usage rates (e.g., total mass sold) and potency to guide the selection
541 of those to include in targeted monitoring in order to gage their potential frequency and extent of
542 occurrence in the environment. In terms of accounting for bathing as a source term in fate

543 models, another source of APIs on the skin to account for is the residue remaining after the
544 removal of a transdermal device such as a patch.

545 Among those topical/transdermal medications with no oral equivalents and which also have
546 minimal excretion (of the absorbed dose), those sharing common mechanisms or modes of action
547 (and for which dose addition might therefore be an important exposure consideration) could
548 prove to be the most important with respect to environmental hazard. The corticosteroids, for
549 example, all affect the hypothalamus-pituitary-adrenal axis, especially those that are not
550 approved for oral or parenteral use. Many of the antibiotics could promote the selection for
551 antibiotic resistance on the surface of skin since their localized concentrations can be extremely
552 high [40, 46].

553 Comparing the mass of API residue remaining in a used delivery device or the residue
554 remaining on the skin, with the mass that would be excreted if the API has been taken orally (or
555 endogenously produced, such as certain hormones), can provide insight as to the relative
556 significance of the pathways. For example, one recently introduced formulation is a metered-
557 dose transdermal spray of estradiol (EvaMist, Vivus) where each metered dose (containing 1.7%
558 estradiol) delivers 1.53 mg of 17β-estradiol. An estradiol gel (Estrogel, Solvay Pharmaceuticals)
559 contains 0.06% estradiol, and a 1.25-g dose of the formulated gel contains 750 μg. The various
560 reference ranges for urinary excretion of endogenous estradiol (assuming no deconjugation,
561 which can be substantial, [59]) range from 10 to 100 μg/d (depending on the woman's age and
562 health), or up to 30 mg/d (during pregnancy) [60]. Assuming a dermal estradiol absorption
563 efficiency of 17% (24-h absorption reported for Estrogel [61]), one dose of the spray or gel could
564 leave on the skin 1.3 mg or 0.6 mg of estradiol, roughly the endogenous amount excreted daily
565 by 6 to 130 women who are not pregnant.

566 Another example is testosterone. A high-content gel form of testosterone (Androgel, 1%
567 testosterone) has a maximum daily dermal dose of 100 mg of testosterone. Approximately 10%
568 is systemically absorbed. Assuming the remainder (90 mg) is eventually washed from the skin,
569 and assuming that the combined urinary excretion of free and conjugated endogenous
570 testosterone from adult males ranges up to 0.3 mg/d (calculated from Al-Dujaili [62] and Timón
571 Andrada et al. [63]), the daily use of testosterone gel could contribute a mass of testosterone
572 equivalent to that excreted naturally from 300 (90/0.3) males.

573 An example of a dermal drug that also has oral formulations is ketoconazole. Once
574 absorbed, only a fraction of a percent is excreted unchanged, meaning that except for the
575 unabsorbed oral dose, bathing (and disposal) could also be the major source of this API in the
576 environment. To assess the significance of dermal drugs as a contributory route to the
577 environment, the following data would need to be compiled for each: fraction of dermal API not
578 absorbed across the dermis (or residue left on skin after removal of a transdermal device),
579 fraction of oral form not absorbed from the gut, and fraction of API excreted unchanged (as well
580 as in easily hydrolyzable conjugates).

581

582 *Pollution reduction*

583 Possible approaches that might help to reduce the introduction of dermal APIs to sewers
584 prior to bathing include: removal of as much of the product from the skin as possible with an
585 absorbent wipe such as toilet paper or cotton balls and then disposing in the trash; for
586 preparations that have dried on the skin (such as gels), adding an oil (such as olive oil or hand
587 cream) to the wipe might enhance removal; development of hand dispensers for topical drugs
588 that minimize over-application (too large a quantity and/or applied over too large an area), which
589 is difficult to avoid with many topical formulations; development of hand dispensers that permit
590 more accurate dispensing to the target site with minimal wastage or over-spreading; and
591 formulations that improve transdermal flux (which would also allow lower applied doses).
592 Overviews of current and future transdermal systems and technologies are provided by Wilkosz
593 and Bogner [28] and Tanner and Marks [64].

594

595 *APIs commonly used in topical medications*

596 The APIs commonly used in topical medications (excluding drugs delivered by transdermal
597 systems) are listed in Table 3. Except where noted, these are the APIs for which the potential is
598 highest that dermal application (as opposed to excretion) is a source for environmental residues.
599 Some of these APIs are also used in oral and parenteral medications. Annotated in Table 3 is a
600 rough categorization of the portion of an API that can be excreted unchanged. Those remaining
601 APIs in the Table that cannot be extensively excreted, if detected in the environment, would have
602 the higher possibility of having originated from bathing (as opposed to excretion via urine or
603 feces). Of this sub-group of topical APIs, data from environmental monitoring exist only for a
604 select few; these data are compiled in **Table 4**.

While the existing data show these APIs present in waters at sub-µg/L concentrations (except for crotamiton), those that belong to the same therapeutic class (such as the corticosteroids or antibiotics) have the potential for combined action via concentration (or dose) addition. Little is known regarding the environmental occurrence of the corticosteroids, as the first papers appeared only recently [65-67]. Note that clotrimazole is included on the List of Chemicals for Priority Action by the Convention by the OSPAR Commission for the Protection of the Marine Environment of the North-east Atlantic ([68], http://www.ospar.org/documents/dbase/decrecs/agreements/04-12e_List%20of%20Chemicals%20for%20Priority%20action.doc). Also note that both clotrimazole and terbinafine were identified using a QSAR approach as among the top 10 chemical substances targeted for further screening ([69], http://www.environment-agency.gov.uk/commondata/acrobat/p601206trv2_578719.pdf.)

Biopharmaceutics Drug Disposition Classification System

The Biopharmaceutics Classification System (BCS), developed by Amidon et al. [70], is a system for classifying APIs according to bioavailability. The BCS essentially categorizes APIs that are orally administered according to the four combinations of permeability and solubility, because absorption largely depends on solubilization of an API across the intestine. Wu and Benet [71] transformed this system to the Biopharmaceutics Drug Disposition Classification System (BDDCS), which categorizes APIs for oral administration according to the four combinations of solubility and metabolism. The BDDCS categories 1 and 2 are subject to a wide array of metabolic pathways leading to extensive excretion of metabolites, whereas categories 3 and 4 primarily are poorly metabolized and therefore are eliminated unchanged in the urine and

628 bile. A wide spectrum of other variables, such as food intake and its composition, also affect
629 excretion [72]. Wu and Benet [71] state that very few APIs undergo intermediate metabolism
630 (e.g., 50%). They are either extensively metabolized or largely excreted unchanged.

631 The BDDCS categories 1 and 2 are of interest with respect to understanding the significance
632 of APIs that are administered topically as a primary source for the API in the environment. The
633 environmental presence of those topical APIs that do not have an oral or parenteral equivalent
634 will clearly be a direct function of the extent of their intended usage, which then leads to
635 introduction to sewage via bathing. But for those topical drugs that also have oral or parenteral
636 uses, the significance of the topical use will be a function of whether oral and parenteral use is
637 accompanied by extensive metabolism and therefore little excretion of the unchanged parent
638 API. Therefore, APIs in BDDCS categories 1 and 2 will contribute little unchanged parent API
639 to the environment via excretion by urine and feces. The dermal use of these APIs could be
640 responsible for the largest portion of the parent APIs in the environment. Since a trend is
641 emerging for new molecular entities to be highly permeable, poorly soluble, extensively
642 metabolized compounds (BDDCS Class 2) [72], this means that for those new molecular entities
643 designed for dermal and oral/parenteral use, bathing and washing could play increasingly
644 important roles with respect to release of APIs to the environment. This also means that disposal
645 to sewers would have the potential to also grow in importance as a source, if newer drugs will be
646 extensively metabolized. Note that of the dermal APIs listed in Table 4 and that also have oral
647 use, four are listed in categories 3 and 4 by Wu and Benet [71]: acyclovir, neomycin, nystatin,
648 and erythromycin. The primary source for APIs in the environment from these classes will
649 probably continue to be direct excretion.
650

Interpersonal dermal transfer

Considerable residues of APIs on skin (from dermal excretion, from topical application, and remaining after removal of transdermal systems) have the potential for being transferred directly to other persons or to surfaces with which others come into contact. Just as with exposure to APIs via drinking water, for most people this would constitute unexpected, unwelcomed exposure [42].

While direct dermal-dermal contact obviously increases the probability of interpersonal passive transfer, the possibility also exists for indirect human exposure during daily routine activities via dermal contact with surfaces previously contaminated with APIs from dermal products that remain on the hands of those who have personally applied topical drugs. One noteworthy example is hormonal preparations, such as testosterone, progesterone, and estradiol – those that are dermally applied as preparations containing very high concentrations (percent levels) by rubbing onto the skin with fingers or the hand. Even after hand washing, substantial residues can remain, resulting in physiologically significant exposures for others. Indirect transfer might be possible by contamination of inanimate objects (e.g., door handles, telephones, keyboards, plumbing fixtures, clothing, currency, etc.) followed with contact by others. The APIs from all types of medications applied by hand or from devices that are touched (e.g., new and used medicinal patches) clearly have the potential for widespread dispersion by these means.

The propensity for topical medications to get dispersed beyond their application sites was demonstrated over 20 years ago with the use of tetracycline. When topically applied, tetracycline was demonstrated to not remain in its original location, but rather to be transferred to other parts of the body. The degree and pattern of transfer was a function of the original site of application, the individual patient, and especially the vehicle in which the tetracycline was prepared (i.e.,

ointment, cream, lotion, or tincture) [73]. This demonstrated the ease with which dermal applications could be transferred.

Several cases have been reported of incidental, passive dermal transfer from parents to children. For example, androgenic steroids such as testosterone (cream) [74-77] and 4-androstenediol [74] topically applied to adults have resulted in profound physiological changes in children (substantial virilization of boys and girls) after interpersonal dermal contact. The vehicle in which the testosterone is delivered could play a role in the potential for transfer, as an alcoholic gel preparation seemed to prevent even purposeful interpersonal transfer [78]; the same was noted for a gel-form of estradiol [79]. But appreciable transfer resulting from a different gel formulation of testosterone was evident in another study, probably from much longer chronic contact [80]. One hour after dermal application of estradiol, purposeful interpersonal skin contact (for 15 mins), resulted in measurable systemic uptake by a naive recipient, largely because the majority of the initially applied dose remained on the skin surface for extended periods [81].

The ease with which dermally applied drugs can be transferred by contact, and their sustained persistence on the skin even after repeated washing, is shown by the contamination that can be introduced to laboratory analyses. After applying 5% progesterone cream by fingers to the body, simply transferring a sample with a pipet introduced considerable background levels of progesterone, even after the fifth hand washing. Contamination could even occur when using gloves, simply by pulling the gloves from their storage box by gripping a finger tip [82]. The same problem has also been noted for a technician who had been using topical testosterone (in gel form) and performing tests for testosterone. Contamination on the fingers led to very high errant test results [83]; the authors noted that it was not possible to remove all traces from the fingers. Also worth noting is that since residues of those drugs that are topically applied (usually

697 in large quantities) can remain on the skin, and since many APIs are excreted through the skin,
698 unique challenges are posed for environmental monitoring. Stringent quality control measures
699 must be implemented to guard against contamination during sampling, monitoring, and sample
700 preparation; a comprehensive system of blanks is particularly important.

701

702 *Residuals remaining in used delivery systems*

703 Although the topic of drug disposal primarily concerns leftover medications, completely
704 used and partially used medications (especially non-oral delivery systems or devices) also serve
705 as a source of APIs during disposal, as the remaining residuals in their leftover contents can
706 represent a substantial portion of the amount present in new, unused devices. Leftover residuals
707 in delivery devices is an issue only recently suggested as a source term needing further
708 evaluation [3, 84]. This aspect has not been accounted for in source terms for fate models, and
709 would be quite difficult to accommodate in a realistic manner, as the residual quantities would
710 vary immensely depending on the type of device, its duration of use, and patient compliance.

711 These used devices themselves can also serve as a considerable acute hazard, as they are
712 responsible for documented morbidity and mortality due to poisonings from unintended exposure
713 and abuse. As a prime example, consider the list of APIs used most commonly in patch delivery
714 devices designed to administer sustained dermal doses (**Table 5**). This table also shows the mass
715 content per device, a rough estimate of the number of lethal oral doses in an unused device, and a
716 rough estimate of the equivalent number of oral doses required to contribute the same mass of
717 API if the unused device were flushed to the sewer. A major variable in determining the quantity
718 of residual is the conditions under which the device is used. Failure to clean or dry the skin prior
719 to application, for example, impedes permeation of the dermal layer.

720 Of the drugs listed, fentanyl patches (either new or used) have an API content sufficient for
721 roughly up to 10 lethal oral doses in adults. Clonidine, nicotine, and possibly lidocaine patches
722 have roughly sufficient API for multiple lethal doses in children or pets. These patches clearly
723 require special care to ensure fast, secure, and safe disposal. These instances are not reflective
724 the much higher possible incidence of morbidity from exposures to other APIs or lower doses.

725 By using the daily doses and excretion efficiencies for the oral versions, the quantity of an
726 API released to sewers from disposal of a device can be compared with the API released from
727 oral doses. Several devices, if disposed to sewers unused, would contribute the equivalent of
728 thousands of oral doses (after accounting for pharmacokinetic data for excretion of unchanged
729 API): methylphenidate (equivalent to 3,280 oral doses), rivastigmine (1,200), and nitroglycerin
730 (2,667). Others would contribute the equivalent of hundreds of oral doses: clonidine (188),
731 ethynylestradiol (214), oxybutynin (720), norethindrone (192), and norelgestromin (240). The
732 residual content of used patches was available only for fentanyl, where a used patch would still
733 be equivalent to hundreds of oral doses (420) [85]. Some patches would serve as unique
734 contributors to the environment since oral equivalents of their APIs do not exist; these include
735 rotigotine, flurandrenolide, and lidocaine.

736 The residual APIs in transdermal therapeutic systems (or other drug delivery devices
737 designed for external extended release) can represent a substantial portion of the amount present
738 in new or unused devices. It can also be considerable when compared with oral daily doses. This
739 pertains especially to APIs formulated in transdermal and transmucosal devices. For transdermal
740 patches, as an example, the residual is a function of how efficiently the API is absorbed across the
741 skin and how long the patch is left in place. This adds an important but highly variable dimension
742 to calculating the significance of disposal compared with excretion. The amount of API that is

743 retained on the skin surface from transdermal delivery devices can also be appreciable, as inter-
744 dermal transfer of clinically significant amounts from these particularly concentrated areas can
745 then occur between individuals as a result of bodily contact. This has been documented, for
746 example, for estradiol [81], where the authors noted that "clinically significant transfer of topical
747 bioactive drugs can occur."

748 A major concern regarding these devices (as with all APIs reformulated for low-dose
749 extended release) is the purposeful circumventing of the design in order to acquire a high-dose
750 immediate-release drug that can be taken via a direct route (such as by mouth, nose, or
751 intravenous); this is an approach used by drug abusers. Indeed, design of devices to accommodate
752 new delivery forms of APIs already in therapeutic use can lead to diversion and abuse – because
753 of their high content of API [86]. Some APIs pose extreme risks and are tightly controlled under
754 formal restricted-access programs, which impose restrictions on various aspects of prescribing,
755 dispensing, or patient usage in order to reduce the risk of diversion, abuse, and imprudent use
756 [87]. These risks largely fall into three major categories: potential for abuse (e.g., buprenorphine),
757 severe adverse drug reactions (e.g., clozapine), and teratogenicity (e.g., thalidomide, isotretinoin).
758 The latter are two examples of those for which inadvertent exposure must be minimized.

759 The first transdermal therapeutic system was a transdermal patch (incorporating scopolamine
760 for motion sickness), approved by the United States Food and Drug Administration in 1979. This
761 was followed by the development of the nicotine patch. An overview of transdermal systems is
762 provided [88]; the number of therapeutic classes being formulated for dermal transfer continually
763 expands, now including such drugs as psychotropics. Most drugs administered by patch pose four
764 main hazards: potential for abuse of used patches, which can contain acutely toxic residual doses
765 when administered by alternative routes (e.g., oral ingestion), potential for accidental poisoning

766 by used (as well as new) patches, which can be accidentally ingested by infants, toddlers, and
767 pets, when disposed to sewers, used patches can contribute a mass of API equivalent to that
768 resulting from excretion from multiple doses of oral formulations, and residues remaining on the
769 skin after a patch is removed can be substantial, contributing to API release to sewers during
770 bathing or to transfer to others by inter-dermal contact.

771 Delivery devices that usually are not disposed by flushing can also pose eventual exposure
772 hazards, especially if disposed to trash that is landfilled [89]. As one example, Guerts et al. [90]
773 calculated that the ethynylestradiol (EE2) remaining in used vaginal contraceptive rings is
774 roughly 85% of the initial amount, corresponding to roughly 2.4 mg of EE2. This EE2 is then
775 available for accumulating in landfill leachate; the same concern would apply to EE2 implants
776 once removed by a physician. Ethynylestradiol is an extremely potent endocrine disruptor in the
777 aquatic environment, having profound effects in fish populations at concentrations in the low
778 parts-per-trillion range [91].

779 The acute risks posed by used delivery systems containing substantial API residues have
780 been amply demonstrated. Unintentional poisonings and abuse are not uncommon. After 3 d of
781 use, fentanyl patches have been reported to retain 28 to 84% of their original fentanyl content,
782 more than sufficient for a lethal oral dose should the patch be applied dermally on an opioid-naive
783 person or be ingested, for example, by an infant [85]. Note that a new 2.5-mg fentanyl patch
784 contains the equivalent of about twelve 200-µg fentanyl lozenges (which are available in
785 formulations of 200 to 1,600 µg in 200-µg increments). The residue in a used 2.5-mg patch might
786 be equivalent to four to ten 200-µg lozenges.

787 Patches are indeed a known cause of fatal poisonings [92] after intentional ingestion by
788 adults [93] and by children [94, 95], as well as by injection of API extracted from patches [96]

789 and by misuse and abuse of patches by misapplication and inappropriate application in numerous
790 different ways [97]. Used nicotine patches have been ingested and applied dermally by children
791 [98]. Used patches may be more likely than new medications to be accessed by children as they
792 can be forgotten once removed.

793 A continuing trend toward designing new and existing APIs in dermal delivery systems
794 could serve to reduce the ameliorative role that metabolism would normally play in reducing the
795 load of APIs in the environment; the API content of dermal delivery systems is also often much
796 larger than required for oral doses. This trend could increase the significance of used and unused
797 leftover medications as a source of APIs in the environment, particularly for those APIs that
798 would otherwise be extensively metabolized if consumed orally or parenterally. The unused
799 portion of APIs in delivery devices clearly serves as a reservoir of APIs that may require
800 additional attention with regard to disposal. While flushing might currently be the best alternative
801 for quickly ensuring that used patches are not accessible to others, there are situations where
802 flushing non-soluble materials is problematic, such as with septic systems. Because of its very
803 high potential for abuse or accidental poisonings, used fentanyl patches pose exceptional
804 challenges, as even patches on decedents are known to be diverted and reused [99] and have led to
805 overdose and death [100]. Except for patches, most devices have very low potential for disposal
806 via flushing (inhalers, venipuncture and other injection devices), so their API residues are not
807 prone to immediately entering sewage. One way to reduce the significance of residual APIs
808 remaining in transdermal and topical (e.g., cream and gel) applications is to improve the
809 efficiency of dermal permeation/absorption (via reformulation); this would also allow the use of
810 less API per application, thereby reducing the remainder yet further.

With respect to veterinary practice, the use of medicated feeds can contain substantial concentrations of drugs such as hormonal growth promoters and antibiotics. Unused feed and feed incompletely consumed (e.g., in aquaculture, where large portions sink before being consumed) can contribute residues to the environment [101] or be eaten by non-target animals.

Residuals and the hazards of attempted medication destruction

The desire for methods that consumers can use to render unwanted, leftover medications unusable (prior to disposal) has led to recommendations to alter the physical form of the medication. One example is the SMARxT disposal campaign, which advises: "Pour medication into a sealable plastic bag. If medication is a solid (pill, liquid capsule, etc.), crush it or add water to dissolve it" or “add kitty litter, sawdust, coffee grounds,”([102], http://www.smarxtdisposal.net). But guidance aimed at altering or destroying medications poses acute hazards for people and pets and also possibly facilitates the entry of APIs to the environment.

Practices that attempt to render medications unusable by physical alteration not only do not prevent diversion to drug abusers – who can easily reclaim the APIs – they also pose additional risks. The need for new approaches for safe and environmentally prudent drug disposal has been discussed [8]. The magnitude of leftover medications has been documented in a number of publications, a recent one being De Bolle, et al [103].

A form of medication alteration long used in medical care is a common practice known as dose-form modification, used especially in long-term care facilities where patients often refuse oral medication or have difficulty swallowing (dysphagia) [104]. Healthcare professionals often resort to dose-form modification to get these patients into compliance. This commonly involves

crushing pills or opening capsules and transferring to a more easily administered format (e.g., mixing in sweetened food). Dose-form modification is controversial because it has the potential to radically alter the pharmacokinetics of medications that are specially formulated to release APIs gradually (e.g., special-release medication forms such as extended release and delayed release formulations). Physical modification can greatly reduce the time required for an API to reach a maximum plasma concentration, and this concentration can often exceed the threshold for adverse effects, because all of the API is released at once instead of over an extended time (e.g., a 12- or 24-h dose delivered all at once). It is widely recognized by drug abusers that pill crushing can lead to greatly enhanced biological activity [105].

Once crushed, the design of extended release tablets is defeated, making immediately bioavailable their entire contents of APIs. Those opiate medications containing APIs that are extremely potent can contain up to several lethal doses per pill for those who are opioid-naive, especially children. While documented reports of harm to patients by healthcare professional are few (most likely because professional healthcare workers are aware of those medications, such as cytotoxics and teratogens, that pose the greatest hazard if modified), the potential clearly exists. Some tablets are specially coated not to modify the absorption or release characteristics, but rather to prevent dermal contact or pulmonary exposure when handling. Breaking this coating poses an acute hazard to anyone in close proximity; residues can then disperse to the surrounding environment. Examples include cytotoxics (e.g., methotrexate, tamoxifen), steroids, prostaglandin analogs, and other hormones. An updated compilation of medications that should not be crushed, not just for therapeutic reasons, but also for safety concerns, is available at the Institute for Safe Medication Practices website ([106], http://www.ismp.org/tools/donotcrush.pdf.). An example of the cautions issued on this website include the one for finasteride (Propecia® and Proscar®,

Merck) and dutasteride (Avodart®, GlaxoSmithKline): "drug may cause fetal abnormalities; women who are, or may become, pregnant, should not handle capsules; all woman should use caution in handling capsules, especially leaking capsules." Oxymorphone (Opana ER®, Endo), oxycodone (OxyContin®, Purdue Pharma) and tramadol (Ultram ER®,Ortho-McNeil Pharmaceutical) users are warned, "tablet disruption can lead to rapid release and absorption of a potentially fatal dose of oxymorphone, oxycodone, or tramadol." The website offers advice about handeling Hydroxyurea (Droxia and Hydrea, Bristol-Myers Squibb) capsules: "exposure to powder may cause serious skin toxicities"; and lenalidomide (Revlimid, Celgene) capsules, calling it a "teratogenic analog of thalidomide."

While some of the dangers in the practice of physical drug destruction pertain solely to the administration of healthcare, some are also pertinent to the relatively recent recommended practice of crushing leftover, unwanted medications in order to facilitate their disposal, such as these instructions on the SmartRx website: ([102], http://www.smarxtdisposal.net): "Pour medication into a sealable plastic bag. If medication is a solid (pill, liquid capsule, etc.), crush it or add water to dissolve it." The intent of this recommendation is to render the medication useless to others so that disposal via trash does not lead to subsequent diversion by others. The consumer, lacking the knowledge of a healthcare professional, would probably not be aware of those medications that would pose acute risks from mechanical alteration – such as by crushing or opening capsules. The average consumer really has no way to know which pills are safe to mechanically destroy and which are dangerous – without carefully reading manufacturers' instructions. Many drugs could possibly be safely crushed (with the proper equipment), but since many should not be altered, comprehensive guidance for disposal would get complicated, as it has always been with respect to the ultimate route of disposal, where certain select medications (e.g.,

those with extreme toxicity or potential for abuse) should still be flushed into sewers to prevent unintended poisonings [23, 107]). Any additional handling of medications, beyond what is needed for therapeutic use, poses added risks for those in proximity and for the environment.

Crushing tablets or opening capsules by the consumer should also be discouraged for a variety of other reasons in addition to the immediate hazard to the person disposing of the medication in this manner. Some of these medications are formulated expressly to resist crushing. Mechanical destruction of medications can be time consuming and difficult. Some tablets can be extremely difficult to crush because of coatings or other properties designed purposefully to prevent alteration (making them physically impenetrable), and capsules can resist disassembly. Frustration could cause the consumer to rush the process or use excessive force, and as a result, disperse or spill dust, particles, or entire pills into the air, on the floor, countertop, or other surfaces or containers that might come into contact with food or beverages; sudden crushing of capsules could expel liquid contents. The dispersed API (or misplaced pills) could then come in contact with pets, infants, toddlers, and other unsuspecting people, where dermal, oral, and pulmonary exposures could occur.

Few consumers even have a mortar and pestle, much less a device specially designed to crush pills, such as those sometimes used in healthcare. They therefore will resort to any number of other improvised approaches, all of which require manual strength and dexterity, and which greatly increase the chances of local area contamination via spillage or dispersal: hammers, knives, pill splitters, spoon bottoms, nested spoons, rolling pins, etc. If a dedicated crushing device is used, it might also serve double duty for subsequent food preparation (e.g., a mortar and pestle used for spices) or eating (e.g., a spoon or cutting board). Yet another exposure pathway is then created. Consumers are often creative, and might also resort to other methods such as food

903 blenders; we have even handled an inquiry from a consumer who had planned to bake their
904 medications in an oven, a practice that could result in pulmonary exposure to highly toxic
905 chemicals. Once the hazards are understood, for consumers still wishing to crush pills, perhaps
906 the best economical approach would be to use a heavy-duty commercial device specially designed
907 for the purpose of crushing ([108], http://www.abinn.com) and where the crushed medications are
908 collected directly into a plastic bag, thereby preventing accidental dispersal. For healthcare
909 workers who want to dispose of larger quantities by crushing, electric automated crushers are
910 available with automatic containment.

911 Furthermore, encouraging the consumer to mechanically destroy or to make unpalatable
912 medications disposed via trash, "Mix drugs with an undesirable substance, such as cat litter or
913 used coffee grounds...." ([23],
914 http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf), may only provide
915 an illusion of preventing reuse and diversion. Addicts and those who abuse drugs are known to be
916 extremely persistent and clever at reclaiming drugs from all sorts of dirty matrices [105]. Any
917 additional step or manipulation recommended for disposal of leftover medications incurs
918 additional risk that medication can fall unnoticed onto floors or counters. Mixing with other
919 substances (such as cat litter) prior to trash disposal is also not without controversy in the
920 pharmacy community [109]; mixing with used cat litter also poses a risk of exposure to pathogen-
921 laden dust.

922 The continuing need to flush or destroy those medications (both new and partially used) that
923 are prone to diversion and abuse could possibly be avoided with advancements in formulation
924 technologies for these drugs. There are a number of approaches under development; several, for
925 example, are specifically designed to deter abuse of oral-use opiates [110]. Some examples

include: formulations that resist crushing and dissolving to obtain an injectable form, where the API is released very slowly and dissolving does not yield an injectable form (the oxycodone formulation Remoxy®, Pain Therapeutics) is an example; formulations having additives that cause unpleasant side effects if taken orally at supratherapeutic doses or if administered by a non-therapeutic route such as by injection or nasally (an example is the oxycodone formulation Acurox®, Acura Pharmaceuticals); and an approach that uses an opioid antagonist (such as naltrexone) in an indigestible form that cannot be absorbed if taken orally as designed, but which is readily released if the medication is crushed. An example is the Embeda® (Alpharma) formulation of morphine.

The literature often mentions the use in Britain of drug destruction kits, usually referred to as DOOP kits, sometimes called controlled drug destruction (or denaturing) kits. While DOOP stands for Destruction Of Old Pharmaceuticals, the process employed has nothing to do with actual destruction or denaturing of the API chemical structure, but rather refers to the physical form of the medication. The process involves physically destroying the medication (e.g., crushing pills or emptying capsules) and mixing with a liquid that solidifies and serves to merely encapsulate the APIs. The point of emphasis here is that this approach would not, as its name implies provide a means for consumers to destroy APIs.

The chemical destruction of APIs has been investigated as an alternative approach to incineration and for dealing with small quantities of waste drugs, especially the highly toxic antineoplastics ([111], http://www.who.int/injection_safety/toolbox/docs/en/waste_management.pdf; [112], http://www.noharm.org/library/docs/NoIncineration_Medical_Waste_Treatment_Techn.pdf). These approaches have generally involved the use of concentrated acids and oxidants, such as

permanganate, sodium hypochlorite, hydrogen peroxide (also with iron - Fenton's reagent), sulfuric acid, nitric acid, and hydrochloric acid. They also usually involve heating and are quite hazardous. Different methods seem to be required for different APIs. One universal approach for all APIs has never been proposed. Often proposed as a means of on-site destruction of APIs at drug collection events (with the intent of permitting the return of controlled substances), chemical destruction is not yet feasible for widespread implementation because of: the hazardous nature of the procedures, the fact that the complete destruction of all APIs cannot be assured (a Drug Enforcement Administration requirement for controlled substances), and the unknowns with regard to the possible generation of hazardous by-products (especially those that are volatile) as a result of multiple APIs undergoing many reactions simultaneously. Greener, less-hazardous destruction methods are just beginning to be developed. These use comparatively less-hazardous reagents and generate much less hazardous waste. One example is the use of an iron-tetraamidomacrocyclic ligand (Fe-TAML) in conjunction with hydrogen peroxide, which has proved highly effective at destroying a variety of APIs, such as estrogens [113]. Another might be the use of electrolysis [114].

Certain drugs should not be unnecessarily handled or altered by consumers, especially those that are considered hazardous. In an occupational setting, hazardous drugs should be handled only when proper containment of dusts, particles, and vapors is sufficient. Crushing tablets or opening capsules containing hazardous drugs should be avoided, even by compounding pharmacists and other healthcare professionals; this points to the heightened hazards that pill alteration could pose to untrained and ill-equipped consumers. Overviews of hazardous drugs and guidelines for their proper and safe handling are available ([115], http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf; [116, 117]). A subset of these pose

risks with respect to dermal or pulmonary exposure (via particulates, dusts, or powders), although for healthcare workers, dermal contact with these drugs (from patients or other sources) is a primary route of exposure, possibly via subsequent hand-to-mouth contact [117].

In the U.S., unintentional poisoning by medications is a leading cause of injury in children (ages 18-35 months). The types of medications commonly involved with poisonings are summarized by Meyer et al. [118]. These are among the medications for which mechanical alteration would pose the highest risk as a result of inadvertent dispersal of particles or whole doses. Those drugs commonly involved with non-life threatening poisonings include: antibiotics, ß2 agonists and sympathomimetics (e.g., phenylephrine and ephedrine), and non-steroidal anti-inflammatories (e.g., mefenamic acid and phenylbutazone). Those involved with a high potential for adverse effects include: antihistamines (H1 and H2 receptor antagonists), beta-blockers, calcium channel blockers (e.g., dihydropyridines such as nifedipine), phenylalkylamines such as verapamil, benzothiazepines (e.g., diltiazem), digoxin, isoniazid, sulfonylureas, and tricyclic antidepressants. Those with the potential for life-threatening effects from even small doses (such as the equivalent of a single, non-delayed release tablet) include: calcium channel blockers, chloroquine/hydroxychloroquine, clonidine, clozapine/olanzapine, flecainide, imidazolines, loxapine, opioids, phenothiazines (thioridazine and chlorpromazine), quinine, sulfonylureas, theophylline, and tricyclic antidepressants (amitryptyline, imipramine and desipramine); also see Bar-Oz et al. [119]. Still others are noted for delayed effects that might not be immediately noticed: diphenoxylate and atropine, hypoglycemic agents, monoamine oxidase inhibitors, and acetaminophen (larger quantities).

Some caveats are also important regarding the guidance issued by manufacturers and others [23, 107] on the disposal of certain hazardous medications by the consumer. The manufacturer's

instructions themselves can cause confusion. One example is the disposal of fentanyl formulated in transmucosal delivery systems such as oral (buccal) lozenges or handles (lollipops). The residue that remains on the handle itself (which should not be flushed) or in partially used lozenges varies greatly, but can be hazardous. Disposal instructions call for dissolving the residue of partially or completely used doses by holding under running hot water. An opiate-naive person could possibly absorb a toxicologically significant dose of fentanyl through the skin (especially if open wounds were present) if partially used lozenges or handles were held with exposed fingers during this process.

A final concern regarding destruction prior to disposal via trash is if someone were poisoned by accidental or purposeful ingestion of crushed pills reclaimed from the trash or from spillage, it would not be as simple and fast to identify the responsible medication as it would be if the intact medication (with identifying information) were available.

Disposal

The wastage caused by unused, leftover medications was recognized as early as the 1970s with some evaluations of the types and quantities of medications returned by the public [120, 121]. The processes developed over the last three decades for handling drug waste generated by consumers has varied greatly among countries [3, 10, 11]. In the U.S., despite federal guidelines ([23], http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf), confusion and debate surround what constitutes the best approaches for disposal ([24, 122], http://blog.epa.gov/blog/2008/12/08/qotw-prescription-drug-disposal).

The overall significance of disposal of medications with respect to its contribution of individual APIs (and APIs in general) is an unresolved question [15]. The information needed to

make this type of assessment has not been available. Here we refer to the relative significance of disposal (versus excretion) as the relative environmental footprint (REF) of a disposed drug. As used here, the REF does not refer to the impact in the environment of the API, but rather to the potential importance of disposal. The REF for disposal is a simplified form of the more comprehensive relative significance (Sr) factor discussed earlier.

Similar to Sr, a disposed drug's relative environmental footprint (REF_d) is a function of two factors: the fraction of overall API mass (or moles) disposed via sewers, and the fraction of API that is excreted unchanged (and/or washed from the skin). The REF_d for a particular API is defined as the contribution of an API to sewage by disposal relative to that released from intended usage (such as via excretion). This can be calculated on the basis of either mass or moles of API as:

$$[\text{fraction disposed}]/[\text{fraction excreted}] = REF_d \qquad (3)$$

Here are some hypothetical examples. Assuming that 10% of an API is excreted and 5% is disposed, then disposal of 1 dose would be equivalent to consuming 0.5 doses with respect to the introduction of the API to sewage. Similarly, assuming that 80% of an API is excreted and 5% is disposed, then disposal of 1 dose would be equivalent to consuming 0.06 doses. With 1% excreted and 5% disposed, disposal would be equivalent to consuming 5 doses. And with 0.01% excreted and 95% disposed (e.g., the remaining residue retained in the container/dispenser), disposal would be equivalent to consuming 9,500 doses. The latter example might emulate the case for an API that was used almost exclusively in topical preparations (and with nominal systemic absorption), which would then be washed from the skin during bathing. So the possible range for REF_d values can range from near zero (where disposal is a non-factor in contributing an API to the environment) to extremely high (where disposal is a major factor).

1041 While REF_d provides the relative potential contributions by disposal among APIs, in order to
1042 gain an understanding of the actual magnitude of API release via disposal, the REF_d must be
1043 multiplied by the actual number of doses sold or dispensed (during a defined period of time):
1044 When multiplied by the number of doses (ND), the REF_d for a particular API yields the
1045 hypothetical number of consumed doses that would be required to release the equivalent amount
1046 of API actually contributed by disposal:
1047 $REF_d \bullet ND/time$ = equivalent doses contributed by disposal during a defined time period (4)
1048 The number of doses must be calculated on the basis of the same units as REF_d (either mass
1049 or moles). Note that when ranking drugs according to REF_d equivalent doses, the relative ranking
1050 could change depending on whether the REF_d is calculated on the basis of mass or moles; low-
1051 molecular-weight APIs would yield larger numbers of doses when expressed in terms of moles,
1052 and high-molecular-weight APIs yielding more doses when the REF_d is expressed in terms of
1053 mass.
1054 A ranking of REF_d values for various APIs would not necessarily be in the same order as the
1055 ranked actual contributions. For example, disposal of a high REF_d API for an infrequently
1056 prescribed medication might contribute less API than a medication whose REF_d is comparatively
1057 very low but which is frequently prescribed.
1058 The variance in the REF_d for a given API will be most affected by the rate of disposal, which
1059 could vary wildly as a function of many variables [8]. The rate of disposal might be most affected
1060 by the type of drug or its therapeutic class, some of which have much greater rates of non-
1061 compliance than others. The REF_d could allow inter-comparisons of drugs to determine the
1062 relative importance of disposal with respect to contributing to the occurrence of their respective
1063 APIs in sewage. By converting numbers of doses to daily doses in terms of mass or moles, a

direct relationship with potency can be obtained. If human potency were assumed to correlate with the potential for ecological effects, then REF_d could be used to reveal which APIs are being disposed in amounts having the highest potential for ecological effects.

The REF_d can be understood best by considering some extreme examples. A drug that is disposed in relatively large quantities can nonetheless have a comparatively low REF_d if its overall use is comparatively larger and/or if it is excreted largely unchanged (extensively excreted). A drug that is disposed in relatively small quantities can have a comparatively higher REF_d if its overall use is comparatively smaller and/or if it is extensively metabolized (leaving little to be excreted unchanged). For an extensively excreted API, both disposal and excretion contribute equally to the environmental loading of the API (each pill disposed contributes to the environmental load the same as if the pill were ingested). For externally applied APIs that are poorly absorbed, the significance of disposal is a direct function of the portion disposed versus the portion absorbed after its designed use (each dose disposed contributes to the environmental load the same as if the dose were applied externally as intended but not absorbed).

The two extreme scenarios that maximize and minimize the significance of disposal are, respectively: disposal of a large fraction of an API that would otherwise be extensively metabolized, and disposal of a small fraction of a drug that would otherwise be excreted largely unchanged (or of topical drugs that are poorly absorbed). The former is exacerbated when the API is purchased in large quantities, and the latter is attenuated yet further when the API is purchased in small quantities.

Five generalizations can be made. Disposal of APIs that would otherwise be extensively metabolized will tend to be responsible for larger percentages of the API in the environment. Disposal of APIs that would otherwise be extensively excreted unchanged will tend be

responsible for smaller percentages of the API in the environment. Models that use the default assumption of extensive excretion (no metabolic conversion) for APIs that actually undergo extensive metabolism will greatly underestimate contributions from disposal. For APIs applied dermally or by delivery devices, the significance of disposal is a direct function of the portion disposed versus the portion absorbed after intended usage. The REF_d is maximized when 100% is disposed and/or 100% is metabolized (none excreted unchanged).

Three major questions could be addressed with this approach. For those APIs that are most frequently detected by environmental monitoring (and in the highest concentrations), do they also have high REF_d values? These might have higher contributions from disposal. For those APIs that are monitored for but rarely detected, are they also among the ones with the lower REF_d values and that are extensively metabolized? These might have little contribution from disposal. Are there APIs with high REF_d's that have never been monitored for? If so, these might be likely targets for monitoring. If detected at critical concentrations, these are also the drugs that might be likely targets for stringent controls on disposal.

Dermal excretion, dermal application, disposal, and lack of absorption from the gut may well explain the presence in sewage of those APIs that are otherwise extensively metabolized; note, however, that this does not take into consideration the extensive conjugation that many drugs undergo, which can be followed by bacterial deconjugation to return the parent drug [59].

In fact, alternative sources of API pollutants that have attracted little attention (such as dermal application, excretion via sweat, and disposal to sewers) may have already served to confuse the conclusions reached by some regarding the presence of certain APIs in the environment. For example, Jjemba [123] reported a possible negative correlation (based on a very small data set) between the efficiency of excretion of an API in its unmetabolized, parent form

and its occurrence in the environment: "the drugs that have a low proportion of the parent compound excreted also display a higher concentration in the aquatic environment". Noted was the widespread occurrence of poorly excreted APIs (e.g., acetylsalicylic acid [aspirin], ibuprofen, acetaminophen [paracetamol], and carbamazepine), as well as some moderately excreted APIs (e.g., sulfamethoxazole, diclofenac, primidone, and rinitinide [*sic*, ranitidine]). All but three of these, however, are available OTC and are purchased in large quantities, which makes them prone to expiration and subsequent disposal. Ibuprofen, acetaminophen, and diclofenac have been reported as among the unused drugs most frequently returned to pharmacies by consumers [124]. Since drugs returned to take-back events currently represent such a small percentage of those that are otherwise disposed to sewers and trash, this poses the possibility that perhaps even larger quantities of these drugs are disposed to sewers. Indeed, in Ruhoy's study of medication disposal inventories assembled from a coroner's office ([125], http://environment.unlv.edu/abstractsGrad/ruhoy.html) acetaminophen and ibuprofen were the first and ninth most abundant medications disposed over a 1-year period (S. Ruhoy, unpublished data). Both are extensively conjugated or oxidized with little unchanged API excreted. The negative correlation noted by Jjemba [123] might simply be the result of not considering all of the possible sources.

Another example is the fifth-most abundant API disposed in the inventory of coroner data conducted by Ruhoy (unpublished data), carisoprodol. Extensive metabolism yields at least three active metabolites (one of which is meprobamate); only traces of carisoprodol appear in the urine [126]. Despite being extensively metabolized, carisoprodol has been reported in several recent monitoring studies. It was even reported at 129 ng/L in recycled water [127]. It was the only API identified in recycled water (at up to 217 ng/L), and also reported in secondary effluent

([128], http://www.valleywater.org/website/media/pdf/Streamflow%20AugmentationDraft%20IS%20MND.pdf). It has also been tentatively identified in runoff from fields irrigated with treated wastewater or effluent-dominated stream water [129]. Note, however, that some conditions can cause the excretion of unchanged carisoprodol (as with many other APIs); these include concurrent administration of APIs that inhibit microsomal oxidases, certain polymorphisms in microsomal oxidases, and stress, which reduces absorption from the gut. Nonetheless, carisoprodol is an example of an API for which disposal might be playing a dominant role in its environmental occurrence.

Disposal of problematic medications

The continuing need in the U.S. to dispose of certain medications by flushing to sewers and actively avoiding disposal in the trash [23, 107], at least until sustainable take-back or collection programs are developed, poses a dilemma in balancing the protection of human health and safety with protection of the environment [16]. These are the highly hazardous medications or those subject to abuse that could be diverted or accidentally acquired if they were disposed in the trash. The potential significance of disposal by flushing can be evaluated by examining the pharmacokinetics of this subgroup of medications to determine the fraction of the API that is excreted unchanged. But two other factors are also required to determine the relative significance of disposal among APIs: the total amount of drug purchased and the fraction eventually disposed (**Table 6**).

In the absence of data for these two factors, a preliminary idea can be formulated as to which drugs that currently require flushing are contributing the highest percentage of APIs to the

environment. An expanded list of drugs (but still not comprehensive) where disposal via flushing is recommended [107] is shown in **Table 7**. These are annotated with information regarding whether they are extensively metabolized or excreted unchanged.

If the efficiency with which an API is excreted unchanged is high, then contributions by disposal would have comparatively less impact (unless an inordinate percentage of the drug is disposed versus actually being used; for example if a medication experiences inordinate non-compliance among patients). On the other hand, if the excretion efficiency is very low (extensive metabolism), then disposal might play an important contributory role. These would be the drugs that could be targeted for alternative approaches for safe disposal should their APIs prove hazardous for the environment.

The sub-group of drugs (those where sewer disposal is still recommended) for which disposal has the potential to play a dominant role in contributing to environmental residues is annotated in Table 7. Note, however, that this assessment ignores the possible contributions from hydrolyzable conjugates or bioactive metabolites excreted in urine/feces. From this assessment, the limited sub-group for which disposal might play only a minor role as a source of APIs in the environment include: entecavir (Baraclude®, Bristol Myers Squibb); oxymorphone (Opana®/Opana ER®, Endo Pharmaceuticals); buprenorphine (Suboxone® & Subutex®, Reckitt Benckiser); gatifloxacin (Tequin®, Bristol Myers Squibb); telbivudine (Tyzeka®, Novartis Pharma Stein AG) and stavudine (Zerit®, Bristol-Myers Squibb).

These are the medications whose continued flushing would most likely contribute the *least* to environmental loadings for the APIs they contain. Until suitable disposal alternatives are available, consideration could be given to continue advising the flushing of these drugs in order to ensure they do not contribute to poisonings or abuse. Human safety concerns (from unsecured

disposal, such as in trash) might clearly outweigh the probably negligible risks for the environment (from disposal to sewers).

This approach, however, only conveys the potential role that disposal could play. Two other factors required in determining the significance of disposal are the fraction of total drug purchased that is eventually disposed and the overall usage rate of the medication (Table 6). Unfortunately, disposal data are very rare. Disposal data were collated from the records collected and maintained by the Clark County Coroner (Las Vegas, NV, USA) using the approach described by Ruhoy and Daughton [3]. These data are located in last column of Table 7. By cross checking the two sets of data (i.e., the potential for disposal significance, based on PK data, versus actual disposal data), the following drugs are the ones that are disposed in the largest quantities (in Clark County Nevada over a particular one-year period) and which also have the potential for contributing the larger portions of APIs to the environment: morphine sulfate extended-release (Avinza®, Ligand Pharmaceuticals); meperidine (Demerol®, Sanofi-Synthelabo); methadone (Dolophine®, Roxane Laboratories); oxycodone (OxyContin®, Purdue Pharma and Percocet®, Endo Pharmaceuticals); and atazanavir (Reyataz®, Bristol-Myers Squibb); morphine is excreted largely as conjugates, and therefore disposal's contribution might not be appreciable. These are the medications for which alternative disposal practices (other than flushing) might be beneficial for the environment. Note that in 2008, the manufacturer re-labeled Reyataz and Baraclude and no longer recommends flushing [130].

Note that fentanyl, although not in the coroner's inventory in substantial quantities, would also be among the drugs where disposal to sewage could prove to be an important source, since it is extensively metabolized. Also note that for drugs administered via a delivery device (e.g., patches, lollipops) or dermally, there will always be additional wastage (residue remaining in the

device). These residues, which can be substantial for patches or partially used lozenges, essentially serve as another contributor analogous to disposal.

For those drugs in Table 7 that were not recovered in the coroner inventory (buprenorphine, diazepam, didanosine, entecavir, methylphenidate, oxymorphone, sodium oxybate, telbivudine), this could indicate that these drugs are sold in very small quantities or that patient compliance tends to be very high – either scenario not promoting leftovers. For these drugs, guidance to dispose by flushing may be inconsequential with respect to environmental impact resulting from excreted residues. It is important to emphasize that these assessments are based on only one study of actual disposal practice and need to be corroborated by further studies (e.g., using data collected from coroner offices in other locales).

Conclusion

It has been long assumed that the active ingredients from human pharmaceuticals (APIs) enter the environment as trace pollutants primarily as a result of their excretion via urine and feces. Urine conveys portions of the APIs that escape metabolism as well as conjugates that are susceptible to later hydrolysis (returning the parent form of the API) and other metabolites (some of which can be highly bioactive). The feces convey metabolites excreted via the bile as well as those portions of APIs that are not absorbed from oral medications.

For the first time, several alternative routes for the entry into the environment by way of sewage have been shown to possibly be important for certain APIs (or therapeutic classes) having particular pharmacokinetic parameters or usage characteristics. These routes include: release of APIs from skin during bathing and washing (those applied topically or transdermally as well as those excreted to the skin via sweat), disposal of unused, leftover medications, and disposal of

used and partially used medical devices, especially transdermal delivery systems. The published literature relevant to these alternative routes has been compiled for the first time, and examples of drugs for which these routes are possibly important are presented.

Routes other than drinking water and foods by which humans can be directly and inappropriately exposed to chronic and acute doses of APIs are also discussed. These include: direct interpersonal dermal transfer; indirect exposure via contact with items touched or used by those who are medicated (e.g., door knobs, telephones, clothing, spas), accidental exposure (such as ingestion by infants, toddlers, or pets) and inappropriate reuse (or abuse) of used or partially used transdermal devices, and unintended exposure to dust, particulates, and scattered pills/capsules that consumers unwisely attempt to destroy (such as by crushing, a recommendation made by some organizations wanting to keep abused drugs from being diverted) before disposing in trash. Some of these routes are documented as leading to morbidity or mortality. All of these routes are interconnected in the lifecycle of APIs in the environment (see Fig. 1).

The unifying concept of pharmEcokinetics was introduced as the umbrella under which the interrelationships can be understood. Some of the vulnerabilities in the lifecycle of an API present opportunities for pollution prevention, an example being more efficient and better targeted delivery of transdermal APIs; proper education of patients by prescribers and pharmacists regarding the application of topical products might also help to reduce over usage. Current recommendations regarding the disposal of certain highly abused drugs by flushing into sewers may not contribute substantially to APIs in sewers; until disposal alternatives are made available more prudent than domestic trash, a rationale is presented for the continuation of disposing these particular medications to sewers. Predictive models that assume extensive excretion for APIs that actually undergo extensive metabolism will greatly underestimate the significance of disposal.

There are many variables that determine the overall significance of these secondary transport and exposure routes. While none of these routes has been realistically factored into published exposure, transport, or fate models (other than in a general way, using generic assumptions), the present study should facilitate the collection of the needed data to make models more accurate and useful, especially for basing decisions involved with pollution prevention or source control.

Acknowledgment–Ilene Ruhoy thanks David Hassenzahl, University of Nevada, Las Vegas for continued guidance, and the U.S. Environmental Protection Agency for granting an appointment as a U.S. EPA Student Volunteer. We also thank Sheila King (Senior Environmental Employment Program, United States Environmental Protection Agency, Las Vegas) for her diligent maintenance of the EndNote PPCPs Literature Database. The authors greatly appreciate the efforts of the three anonymous reviewers, who invested considerable time and thought in providing extensive comments that greatly improved the quality of the final product.

The U.S. Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to the Agency's administrative review and approved for publication as an U.S. EPA document.

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1712 **Figure Legend**

1713 FIGURE 1. PharmEcokinetics of Active Pharmaceutical Ingredients (APIs).

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Table 1. Factors Determining the Significance of Disposal and Washing or Bathing in the Discharge of Active Pharmaceutical Ingredients (APIs) via Sewers [a]

Factor	Term	Importance to Contributing APIs	Relevant Information
Usage rate	*UR*	Total mass or moles of API consumed per time period (mass/time). Disposal of little-used medications contributes insignificantly to the overall combined levels of APIs in the environment, regardless of the portion disposed. This contrasts with disposal of small portions of medications that are used in large quantities.	Usage includes prescribed and (OTC) amounts that are: (1) purchased in-country (including gray and black markets), (2) distributed for free (e.g., physician samples; community programs for indigents; charitable contributions from manufacturers), and (3) imported from other countries. One complication (discussed in the text) is that sales and disposal are not linked in time. Disposal always occurs from sales made in the past. This time lag can also vary, forcing gross simplifications for the purposes of modeling.

Disposal potential	*DP*	Portion of total API left over versus amount that was meant to be totally consumed as directed.	One complication is the portion of leftover drugs that are indefinitely stockpiled, never disposed. Also requiring disposal are used delivery systems still containing residual APIs (see: Type of delivery system or container, below). The potential for a drug to be disposed is probably partly a function of geographic locale and time of year (e.g., for seasonal medications).
Method of disposal	*PDs*	Portion of API disposed to sewers (flushed or poured down drains, such as in-sink garbage disposals) versus all other routes or fates (e.g., trash, burial, collection events, diversion, permanently stockpiled on site, charitable contributions). Note that charitable contribution is a route generally relevant only in controlled healthcare settings, e.g., physician donation of unexpired samples.	How (and sometimes whether) a medication is disposed is partly a function of the design of the medication's packaging. Some packaging (such as unit-packaged drugs) is more amenable to discarding to trash (because of the effort involved in removing from the package in order to flush), while other packaging is more likely to result in disposal to sewers (e.g., bulk-packaged tablets/capsules and liquids); excess medication that remains in delivery devices or delivery systems is also more prone to disposal via trash rather than sewers (see Type of delivery or container, below), although some delivery systems (such as patches) that contain potent APIs (which can cause unintentional poisonings) or those subject to abuse, may still require disposal via flushing. Charitable contributions (and drug sharing) merely postpone the eventual fate of APIs but might serve to reduce the need for new purchases.

Primary metabolic profile	*PMP*	Combined portions of systemic API excreted unchanged into urine and feces and portion of ingested dose not absorbed by the gut. Data come from pharmacokinetics studies. It is important to note, however, that excretion data can be highly variable for a given API and are often difficult to find in the published literature [131].	There are two extremes: (1) extensive metabolism, where little of the parent API [or glucuronides susceptible to hydrolysis] is excreted, and (2) extensive excretion in urine and feces, where the unchanged parent API is excreted, sometimes stoichiometrically; some drugs, such as neomycin, are poorly absorbed after oral or parenteral administration and therefore are excreted largely unchanged because of no opportunity for metabolism (even if the small absorbed portion is extensively metabolized). One complication is excretion of glucuronides having the potential to later be hydrolyzed to products including the parent API; conjugates can therefore often be treated as parent API. Excretion contributes primarily via urine and feces. For APIs that are extensively metabolized, alternate routes to sewers become comparatively more significant.
Secondary metabolic profile	*SMP*	Portion of systemic API excreted unchanged via sweat (and other minor routes such as vomitus).	When excreted via sweat, APIs tend to be excreted unchanged. The relative contributions from sweat compared with urinary or fecal excretion is unknown and comparatively much smaller but measurable for many drugs. The end result is that this portion becomes washed from the skin or transferred by bodily contact to other surfaces (including people).

Route of delivery (bioavailability)	*RD*	Portion of API remaining on skin after topical application (or delivery system). Whether the medication is designed for topical use, where little API is actually absorbed dermally, and the majority remains on the skin. Medications designed for external use efficiently introduce APIs to sewage via bathing or washing (as well as laundering), as if they were disposed directly. These pharmaceuticals serve essentially as inputs tantamount to unintended disposal.	Medications designed for topical use, such as gels, creams, lotions, sprays, tinctures, ointments, plasters, shampoos, foams, powders, and soaps, or for transdermal delivery (where only a fraction is actually absorbed across the skin and a portion is retained on the surface of the skin) are efficiently discharged to sewers as a result of their intended use, via bathing/washing. These medications contribute APIs to sewage as if they were disposed directly. Transdermal patches also leave residual on the skin, residue that will later be washed away as if it had been applied topically.

Type of delivery system or container	*TD*	Portion of dose remaining in delivery system and discharged to sewers. Delivery systems and containers often can have large amounts of residual APIs (some of which remains inaccessible because of the design of the system's device or containers). These residues can then serve as *used* medications that then require disposal.	Drugs administered via delivery devices (e.g., transdermal patches, vaginal rings) can retain very large portions of their total APIs after use is completed because only fractions of their contents are actually delivered systemically (e.g., as little as 15% or less). Containers (e.g., injection vials) and injection/infusion devices can also contain residues. When disposed after use, these can contribute substantial quantities of APIs. These used devices need to be factored in with their unused new counterparts as contributors during disposal. While most new or used devices are not disposed to sewers, some must still be flushed according to the U.S. Office of National Drug Control Policy (ONDCP) guidelines (one example being fentanyl patches)[b]. Important to note is that the very drugs that are subject to waste minimization via charitable donations (as set up by various states) are the same ones that would otherwise most likely be disposed into the trash - not the sewer - simply because of the time and effort required in removing each dose from its packaging. It is most likely that the drugs currently disallowed for donations play the larger roles in disposal via the sewer.

[a] The factors in this table can be used in the following two equations (described in the text):

WM (API mass discharged to sewers from disposal and washing) = UR(mass) • [(DP • PDs) + (SMP + RD + TD)]

Sr (relative overall significance of secondary routes) = WM • $[(UR - WM) \bullet PMP]^{-1}$

[b] ([23], http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf)

Table 2. Overview of Active Pharmaceutical Ingredients (APIs) Measured in Sweat

API or class Chemical Abstracts Service Registry Number, freebase	Concentration (on basis of volume of sweat) or Mass Collected on Sweat Patch or Wipe	Reference
β-lactam antibiotics	Mean maximum concentrations: benzylpenicillin (axilla 2.6 μg/ml) ceftazidime (axilla, 28.4 μg/ml; forearm, 11 μg/ml) ceftriaxone (axilla, 8.9 μg/ml; forearm, 2.5 μg/ml) cefuroxime (axilla, 7.8 μg/ml) phenoxymethylpenicillin (axilla, 0.4 μg/ml)	[46]
aminopyrine (58-15-1) and antipyrine (60-80-0)	extensively excreted via sweat; up to 14 μg/ml after single 1-g oral doses	[132]
amitriptyline (50-48-6)	extensive excretion in sweat after acute poisoning (0.78-0.2 mg/L)	[133]
amphetamine (300-62-9)	median (range) after low and high doses: 15.5 (6.5-40.5) and 53.8 (34.0-83.4) ng/patch	[134]
carbamazepine (298-46-4)	present in sweat extensive excretion in sweat after acute poisoning (3.267 mg/L)	[33] [133]
clomipramine (303-49-1)	extensive excretion in sweat after acute poisoning (0.28 mg/L)	[133]
ciprofloxacin (85721-33-1)	2.2-5.5 μg/mL (during 7-day course of 750 mg/day oral dose)	[40]
cocaine (50-36-2)	33-3,579 ng/patch/30 min (from heat-induced sweating) 43-3,799 ng/wipe ng/mL: cocaine (378), benzoylecgonine (78.7), ecgonine methyl ester (74) up to 315 ng/patch (140 ng/L) during 1 week after nasal doses of 50-126 mg	[135] [136] [37] [137]
codeine (76-57-3)	11-1,123 ng/patch/30 min (from heat-induced sweating) 0-225 ng/patch/week 2-127 ng/patch/day (after 90-mg oral dose)	[135] [138] [139]
clomipramine (303-49-1)	extensive excretion in sweat after acute poisoning: (0.28 mg/L)	[133]
clozapine (5786-21-0)	49 to 5,609 ng/patch in sweat after oral dosing of 200-700 mg/day	[140]
diazepam (439-14-5)	0.1-6 ng/patch total after one dose (first detected 2-4 h after dose; also detected was nordiazepam but not oxazepam) extensive excretion in sweat after acute poisoning	[141] [133]
doxorubicin (23214-92-8)	observed	[47, 48]

fentanyl (437-38-7)	concentrations in sweat varied from 0.17 to 1.02 ng/µl	[41]
fluconazole (86386-73-4)	high concentrations in sweat, all above the serum concentrations	[142]
griseofulvin (126-07-8)	200-300 ng/mL independent of sweat volume; after 0.5-g oral doses at 12-h intervals.	[143]
itraconazole (84625-61-6)	mostly excreted through sebaceous glands; moderately excreted by the sweat glands	[144]
loratadine (79794-75-5)	detectable on skin 40 min after ingesting a 10-mg oral dose	[44]
MDMA ("ecstasy") (3,4-methylenedioxy-methamphetamine) (42542-10-9)	Mean: 542 ng/patch/day; range: 42.4-1,326 ng/patch/day accumulated after single 100-mg oral dose (first observed 1.5 h after dose)	[35]
methadone (76-99-3)	presence correlated with urine detected in sweat of heroin addicts undergoing treatment	[145] [146]
Methamphetamine-HCl (51-57-0)	median (range) after low and high doses: 63.0 (16.8-175) and 307 (199-607) ng/patch constant rate of 1.4 µg/mL after oral dose of 10 mg	[134] [147]
methotrexate (59-05-2)	Mean 725 ng/mL (mean maximal concentration 1.7 µg/mL)	[50]
opiates	median concentrations (ng/mL): heroin (10.5), 6-acetylmorphine (13.6), morphine (15.9), and codeine (13.0)	[148]
phenobarbital (50-06-6) (phenobarbitone)	0.5-33 ng/patch/day (first observed 3 h after 100-mg oral dose) concentration in sweat found to increase with increasing sweat flow	[139] [33]
phenytoin (57-41-0)	concentration in sweat was independent of sweat flow	[33]
sulfonamides	one of the very early studies documenting that drugs are excreted via sweat; sulfapyridine, sulfathiazole, sulfadiazine, and *p*-aminohippurate ranged up into the 10's of µg/ml	[30]
tetrahydrocannabinol (THC) (1323-34-8)	0.9-3.11 ng/patch/day below detection limit after daily ingestion of 14.8 mg	[149] [150]

Table 3. Active Pharmaceutical Ingredients (APIs) Commonly Used in Topical Medications[a]

STEROIDS

Alclometasone dipropionate[b] 0.05%; cream, ointment
Amcinonide 0.1%; cream, ointment, lotion
Betamethasone dipropionate[d] 0.05%; ointment, cream, lotion, gel
Betamethasone valerate[d] 0.12%; foam, lotion, cream
Clobetasol propionate 0.05%; foam, lotion, cream, ointment, gel, shampoo, spray
Clocortolone pivalate 0.1%; cream
Desonide 0.05%; foam, ointment, lotion, gel, powder, aerosol
Desoximetasone[b] 0.25%; cream, ointment, gel
Diflorasone diacetate 0.05%; cream, ointment
Fluocinolone acetonide 0.025%; cream, oil (also vitreal implant)
Fluocinonide 0.05%; cream, ointment, gel, solution
Flurandrenolide 4 μg/cm^2; tape
Flurandrenolide 0.05%; ointment, cream, lotion
Fluticasone propionate[c] 0.05%; cream, lotion, ointment, spray
Halcinonide 0.1%; cream, ointment, solution
Halobetasol propionate 0.05%; cream, ointment
Hydrocortisone acetate[c] 2.5% (with pramoxine HCl 1%); lotion, cream, ointment
Hydrocortisone butyrate[c] 0.1%; cream, ointment
Hydrocortisone (cortisol)[c] 1%, iodoquinol 1%; cream
Hydrocortisone valerate[c] 0.2%; cream, ointment
Mometasone furoate[b] 0.1%; cream, ointment, lotion, spray
Prednicarbate 0.1%; cream, ointment
Triamcinolone acetonide[c] 0.2%; cream, lotion, ointment, aerosol

ACNE

Adapalene 0.1%, 0.3%; gel
Clindamycin phosphate[d] 1.2%; gel, cream, foam, lotion, pads
Erythromycin[d,f] 5%; gel, solution, ointment, swabs
Sulfacetamide, sodium 10%; lotion, ointment, cream, foam, gel, wash, pads
Tazarotene 0.1%; gel, cream
[e] Tretinoin 0.1%; alcohol, gel, cream, solution

SKIN/EYE INFECTIONS

[e] Acyclovir 5%; cream, ointment, solution
Bacitracin zinc 500 Units; ointment
Butenafine HCl[b] 1%; cream
Chloroxine 2%; shampoo
Ciclopirox[b, g] 1%; shampoo, cream, lotion, gel
Ciclopirox[b] 8%; topical solution (nail lacquer)
Clotrimazole[c] 1%; cream, lotion, solution
Docosanol 10%; cream
Econazole nitrate 1%; cream
Ketoconazole[c] 2%; gel, shampoo, foam, cream
Miconazole nitrate 2%; powder, spray, cream, suppositories
Mupirocin 2%; ointment, cream
Naftifine HCl[b] 1%; cream, gel
[e] Neomycin 3.5 mg (with bacitracin zinc 500 Units/g, polymyxin B sulfate 10,000 Units/g); ointment
[e] Nystatin 100000 Units/g; powder
Oxiconazole nitrate 1%; cream, lotion
Penciclovir 1%; cream
[e] Polymyxin B sulfate 10000 Units/g (with bacitracin zinc 500 Units/g or neomycin sulfate 0.35%); ointment, powder, cream
Retapamulin 1%; ointment
Sertaconazole nitrate 2%; cream
Sulconazole nitrate 1%; cream, solution
[e] Sulfadiazine, silver 1%; cream
Terbinafine HCl[c] 1%; cream, solution
[e] Tobramycin 0.3% ointment, solution
Tolnaftate 1%; cream, powder, solution, aerosol

PSORIASIS

Calcipotriene[b] 0.005%; ointment, solution, cream
Salicylic acid 6%; shampoo

WARTS

Imiquimod[b] 5%; cream
Podofilox[b] 0.5%; gel, solution
Salicylic acid 40%; plaster

SCABIES/LICE

Crotamiton 10%; cream, lotion
Lindane[b] 1%; lotion, shampoo
Malathion[b] 0.5%; lotion
Permethrin 5%; cream
Pyrethrins 0.33%, piperonyl butoxide 4%; gel, shampoo, lotion
Pyrethrum extract 0.33%, piperonyl butoxide 4%; oil

ROSACEA

Azelaic acid[b] 20%; cream, gel
[e] Metronidazole 1%; lotion, cream, gel

LOCAL ANESTHETICS

Benzocaine, Butamben, Dibucaine, Lidocaine, Pramoxine, Tetracaine; cream, ointment, gel, lotion

MISCELLANEOUS

[e] Doxepin HCl 5%; cream
[e] Fluorouracil 5%; solution, cream
Nitroglycerin[c] 2%; ointment, solution, patch
Pimecrolimus[b] 1%; cream
Tacrolimus[d] 0.03%; ointment

[a] This listing ([57], http://formulary.prescribingreference.com/dermatological_disorders) excludes those medications that are specially formulated as transdermal systems (e.g., patches).

NOTE: Only the highest concentration in use is listed, which may not apply to all the formulations. APIs used in multiple categories are listed only under the category that uses the highest concentration. Usage and excretion data from: ([151], http://dailymed.nlm.nih.gov/dailymed/about.cfm; [152], http://www.rxlist.com; [153], http://www.druglib.com).

Unless otherwise noted, all APIs are approved only for external use (topical, dermatologic, ophthalmic), having no common off-label oral or parenteral use.

[b] API is used only externally, but a small portion is known to be systemically absorbed and excreted.

[c] API also has oral and/or parenteral use but is extensively metabolized and therefore little is excreted unchanged.

[d] API also has oral and/or parenteral use and a small portion (<10%) is excreted unchanged.

[e] API also has oral and/or parenteral use and is extensively excreted unchanged or as active metabolites.

[a,f] Erythromycin readily undergoes internal dehydration to inactive anhydroerythromycin (erythromycin-H_2O) [154], which is routinely detected in the environment [155].

[b,g] Approximately 10% of ciclopirox dermal dose excreted unchanged over 10 hours ([153], http://www.druglib.com).

Table 4. Topical Active Pharmaceutical Ingredients (APIs) Poorly Excreted but Identified During Environmental Monitoring[a]

API Chemical Abstracts Service Registry Number	Sewage Influent ng/l	Sewage Effluent ng/l	Surface Water ng/l	Biosolids ng/kg dry weight	Reference
Betamethasone (378-44-9) (plus dexamethasone; the two could not be distinguished)	15	7	0.02-0.31		[66] [65]
Clindamycin (18323-44-9)	 80-120	1,000 30	 up to 24	1,540	[156] [157] [158] [67]
Clotrimazole (23593-75-1)	 10-33		up to 22 6-34		[159] [160]
Cortisone (53-06-5) Cortisol (hydrocortisone) (50-23-7)	174 4.6-86 53 7.6-120 370	229 0.13-0.58 63 0.25-1.9 38	 0.06-4.2 0.08-3.4		[66] [65] [66] [65] [161]
Crotamiton (483-63-6)	 1,610	 245-968 580-979	up to 504 6.67 (groundwater) 269-504		[162] [163] [164]

Docosanol (661-19-8)			reported in river sediments (but source might be natural)		[165]
Fluocinolone acetonide (67-73-2)	0.3	11			[66]
Miconazole (22916-47-8)		up to 9 not detected			[160] [166]
Salicylic acid (69-72-7)		25-47 up to 2,100	up to 2,100 370	96,000-253,000	[157] [167] [168]
Triamcinolone acetonide (76-25-5)	40	3			[66]

[a]APIs from Table 3, for which the potential is highest for dermal application (as opposed to excretion) as a source for environmental residues; all of the scabies/lice APIs have been excluded because of their large non-therapeutic usages in pest control.

Table 5. Active Pharmaceutical Ingredients (APIs) Commonly Used in Delivery Devices for Administering Sustained Dermal Doses[a]

API – device (trade name) Chemical Abstracts Service Registry Number freebase	Mass/Device	Daily oral dose (if applicable); unless otherwise noted	Lethal dose	Equivalent lethal oral doses per device	Excretion Efficiency[b]	Equivalent oral daily doses contributing API to environment if device is disposed to sewers (range) [c]
fentanyl - transdermal patch (pain) - UNUSED [Duragesic] (437-38-7)	1.25-10 mg/patch	200 µg/day up to 1,200 µg/day oral	~ 1 mg [85]	1-10 (for 70 kg person)	>90% transformed to N-dealkylated and hydroxylated inactive metabolites	1.25 mg/(1.2 • 0.1) = 10 10 mg/(0.2 • 0.1) = 500
fentanyl - transdermal patch (pain) - USED	reported to retain 28-84% of original fentanyl content [85]			<9 (for 70 kg person)		(1.25 • 0.28)/(1.2 • 0.1) = 3 (10 • 0.84)/(0.2 • 0.1) = 420
clonidine - transdermal patch [Catapres-TTS] (4205-90-7)	2.5-7.5 mg/patch per week	0.1-0.3 mg/day oral	highly toxic with ingestion by child of 0.01-0.04 mg/kg [169]	ca.10-30 (20-kg child)	40-60% excreted unchanged	2.5 mg/0.3 • 0.6 = 14 7.5 mg/0.1 • 0.4 = 188
methylphenidate - transdermal system [Daytrana] (113-45-1)	27-82 mg/patch	2.5-10 mg/day oral; max 90 mg/day	Unknown (children) 2-5 g (adults)	0	Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of dose is excreted in urine as ritalinic acid (60%-86%), the remainder comprising minor metabolites	27 mg/90 • 0.01 = 30 82 mg/2.5 • 0.01 = 3,280
selegiline - transdermal system (depression) [Emsam] (14611-51-9)	20-40 mg/patch	10 mg/day oral	>140 mg [170]	0	extensively metabolized	20 mg/10 • 0.1 = 20 40 mg/10 • 0.1 = 40
rotigotine - transdermal system (Parkinson's) [Neupro] (99755-59-6)	4.5-13.5 mg/patch	NA: not used orally - high clearance and a relatively short duration of effect	> 0.1 mg/ml plasma concentration	0	extensively metabolized	Unlimited
rivastigmine - patch (Exelon) - reversible cholinesterase inhibitor (Alzheimer's; Parkinsons) [Exelon] (123441-03-2)	9-18 mg/patch	1.5-6.0 mg twice a day			extensively metabolized; no parent drug detectable	9 mg/6 • 0.01 = 17 18 mg/1.5 • 0.01 = 1,200

oxybutynin - transdermal (antispasmodic, anticholinergic) [Oxytrol] (5633-20-5)	36 mg/patch	5-15 mg/day oral			extensively metabolized; <0.1% excreted unchanged in urine	36 mg/15 • 0.01 = 240 36 mg/5 • 0.01 = 720
ethynylestradiol (EE2) (57-63-6) with norelgestromin (NGMN) patch (53016-31-2) (contraception) [Ortho-Evra]	6.00 mg NGMN 0.75 mg EE2/patch (per week)	250 µg NGMN/day (1.75 mg/week) 35 µg EE2/day (0.245 mg/week) Female hypogonadism: 0.02-0.05 mg EE2 1-3 times daily for first 2 weeks of cycle. Inoperable progressing prostatic cancer: from three 0.05 mg to four 0.5 mg daily for palliation. Inoperable progressing breast cancer: two 0.5 mg three times daily.			EE2: very low but can undergo extensive deconjugation NGMN: extensively metabolized, but also to active metabolites ([171], http://www.orthoevra.com/orthoevra/shared/shared/pi/OrthoEvraPI.pdf)	EE2: 0.75 mg/0.035 • 0.1 = 214 NGMN: 6 mg/0.250 • 0.1 = 240
17β-estradiol (E2) - transdermal system [Estraderm; Menostar; Esclim; Alora; Vivelle; Climara] (50-28-2)	0.39-1.56 mg/patch	Replacement therapy oral doses ~ 1-2 mg/day (up to 30 mg/day for breast cancer)[d]			10% of oral dose excreted unchanged in urine [173], but can undergo extensive deconjugation; urinary excretion of endogenous estradiol ranges 5-100 µg/day (women), 2-25 µg/day (men), but up to 30 mg/day (pregnant women) [60]	0.39 mg/2 • 0.1 = 2 1.56 mg/2 • 0.1 = 8
17β-estradiol - metered-dose transdermal spray (EvaMist)	each metered dose (1.7%) contains 1.53 mg E2 (1-3 doses per day)	Replacement therapy oral doses ~ 1-2 mg/day (up to 30 mg/day for breast cancer)				1.53 mg/2 • 0.1 = 8
E2/levonorgestrel (797-63-7) - transdermal system [Climara Pro]	4.4 mg E2 and 1.39 mg levonorgestrel	E2: ~ 1-2 mg/day levonorgestrel: 0.1 mg/day			levonorgestrel partly excreted unchanged in urine	E2: 4.4 mg/2 • 0.1 = 22 4.4 mg/1 • 0.1 = 44 levonorgestrel: 1.39 mg/0.1 • 0.5 = 28
E2/norethindrone acetate (NETA) (51-98-9) - transdermal system [Combipatch]	0.62 -0.51 mg E2 and 2.7 - 4.8 mg NETA/patch	0.5 mg of norethindrone			<5% excreted unchanged, but extensively conjugated	NETA: 2.7 mg/0.5 • 0.05 = 108 4.8 mg/0.5 • 0.05 = 192

testosterone - transdermal system [Androderm] (58-22-0)	12-24 mg/patch	50-400 mg (testosterone enanthate, IM) once or twice per month		0	testosterone not usually administered orally (excretion of free and conjugated testosterone from adult males ranges up to 0.3 mg/day calculated from data in [62,63] About 90% given intramuscularly excreted as urine conjugates, and about 6% excreted unchanged in feces.	equiv oral DD = 2.5-5 mg/day (assuming no metabolism) 12 mg/400 • 0.1 = <1 24 mg/50 • 0.1 = 5
diclofenac epolamine - topical patch (pain) [Flector] (119623-66-4)	180 mg/patch	100-200 mg/day oral, of diclofenac HCl		0	little excreted unchanged in urine	180 mg/200 • 0.1 = 9 180 mg/100 • 0.1 = 18
nicotine [Nicotrol; Nicoderm CQ] (54-11-5)	7-21 mg/patch	NA	30-60 mg [174]	<1 (toxic for children)	10-30% excreted unchanged in urine	21 mg/30 • 0.3 = 2
scopolamine - patch (nausea) [Transderm SCOP] (51-34-3)	1.5 mg/patch	oral dose 0.4 mg every 4-8 hours as needed	>2-4 mg	<1	<10% excreted unchanged in urine	1.5 mg/0.4 • 0.1 = 38
flurandrenolide - topical tape (corticosteroid) (1524-88-5)	4 mg/square centimeter	NA				Unlimited
nitroglycerin (angina) [Minitran; Nitro-Dur] (55-63-0)	20-160 mg/patch	~ 3 X 0.6 mg sublingual	>200-1,200 mg [e]	<1	extensively metabolized	20 mg/3 • 0.1 = 67 160 mg/0.6 • 0.1 = 2,667
lidocaine [lignocaine] - patch (5%) [Lidoderm] (137-58-6)	700 mg/patch; 46 mg/mucoadhesive patch	NA	Severe effects >15mg/kg [176]	>2 (20-kg child)	lidocaine: <10% excreted unchanged, but several less-potent metabolites are also excreted; tetracaine: unknown but undergoes rapid hydrolysis	NA
lidocaine/tetracaine (94-24-6) [Synera]	70 mg each/patch	NA				NA
salicylic acid (warts) [Duofilm; Duoplant] (69-72-7)	17% flexible collodion	NA				NA

[a] unless noted otherwise, data from: ([152], http://www.rxlist.com; [153], http://www.druglib.com; [172], Physician's Desk Reference. 2009. Medical Economics Data Production Company, Montvale, NJ, USA.)

[b] extensive metabolism was assumed to equate with 10% of dose excreted unchanged;

[c] (mass contained in device) • [(dose in mass per day) • (fraction of API excreted unchanged)]$^{-1}$; calculated to provide the minimum and maximum possible.

[d] ([172], Physician's Desk Reference. 2009. Medical Economics Data Production Company, Montvale, NJ, USA.)

[e] ([175], STET http://www.spfiles.com/pinitrodur.pdf).

Table 6. Unknowns/Variables in Calculating Relative Environmental Footprint of a Disposed Drug

total consumption	No ready source of data on total quantity of an API consumed (on the basis of either locale or population). Must be derived from sales figures and by making assumptions of average cost per dose and average mass per dose. When using local coroner data [15], this can be derived from the dispensed amounts (but then it must also be known whether the medication was for short-term treatment or long-term maintenance). Multiple medications sharing the same API further complicate calculations.
fraction disposed	Even though coroner data specify the route of disposal, and even if the fraction disposed were known for the larger population, assumptions would still be required as to what portion was disposed via sewage versus trash or take-backs (or stockpiled indefinitely). One complication (discussed in the text) is that sales and disposal are not linked in time. Disposal always occurs from sales made in the past. This time lag can also vary, forcing gross simplifications for the purposes of modeling.
fraction excreted unchanged	Pharmacokinetic data are generally available for nearly all APIs [a], but there are three major caveats: (1) these data are usually acquired from healthy volunteers, and absorption, metabolism, and excretion could differ widely for patients in diseased states or because of gender, ethnicity, age, body weight, diet, and other factors; (2) the metabolism of many drugs yields conjugates, which can be hydrolyzed during sewage treatment or once in the environment, yielding the parent API; and (3) for drugs administered with a delivery device (e.g., patches), the amount of API remaining in the used or partially used device is unknown, and this residue comprises large amounts of fully unmetabolized parent API.

[a] ([152], http://www.rxlist.com; [153], http://www.druglib.com; [172], Physician's Desk Reference. 2009. Medical Economics Data Production Company, Montvale, NJ, USA.)

Table 7. Drugs That Should Be Disposed by Flushing[a]

Drug Tradename Active Pharmaceutical Ingredients (API) [Chemical Abstracts Service Registry Number freebase]	Excretion Efficiency [b]	API Disposed (mg) [c]
[d]Actiq (oral transmucosal fentanyl citrate) [990-73-8]	>90% transformed to N-dealkylated and hydroxylated inactive metabolites	0
[d]AndroGel (1% testosterone gel) [58-22-0]	testosterone not usually administered orally [excretion of free and conjugated endogenous testosterone from adult males ranges up to 0.3 mg/day calculated from data in [62,63] ~ 90% given intramuscularly excreted in urine as conjugates, and about 6% excreted unchanged in feces.]	4,430 total (16 x 5-mg patches = 80 mg 3 x 75-g 1% pumps = 2,250 mg 42 x 5-g 1% packets = 2,100 mg)
[d]Avinza (morphine sulfate extended-release) [64-31-3]	Approximately 10% of morphine dose excreted unchanged in the urine; 7-10% excreted in feces; most excreted as conjugates; but also excreted as the major metabolite of codeine and heroin	103,000
Baraclude (entecavir) [142217-69-4]	predominantly eliminated in urine as unchanged API (62-73% of dose)	0
[d]Daytrana (methylphenidate) [113-45-1]	Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60%-86%), the remainder being accounted for by minor metabolites	0
[d]Demerol (meperidine) [57-42-1]	negligible excretion unchanged ([177], http://www.sanofi-aventis.ca/products/en/demerol.pdf)	81,000
[d]Diastat AcuDial (diazepam rectal gel) [439-14-5]	well absorbed following rectal administration (equivalent of 90% of oral dose); extensively metabolized to conjugates	0
[d]Dilaudid/Dilaudid-HP (hydromorphone) [466-99-9]	extensively metabolized (>95%)	5,870
[d]Dolophine (methadone) [76-99-3]	extensively metabolized	53,480
[d]Duragesic (new and used) (fentanyl) [437-38-7]	*see Actiq*	2.9 total (3 x 25-µg patches 38 x 75-µg patches)

[d]Estrogel (estradiol gel; 0.06%) [a 1.25-g dose contains 750 µg; a new 93-g dispensing pump contains 55 mg; a fully used pump will retain about 10% residual] [50-28-2]	10% of oral dose excreted unchanged in urine [173], but can undergo extensive deconjugation; urinary excretion of endogenous estradiol ranges 5-100 µg/day (women), 2-25 µg/day (men), but up to 30 mg/day (pregnant women) [60]; replacement therapy oral doses < 1mg/day	amount washed from skin and hands (after application/absorption); dermal absorption efficiency is about 17% per day [61]
[d]Fentora (fentanyl buccal tablets) [437-38-7]	*see Actiq*	0
[d]Ionsys (transdermal fentanyl)	*see Actiq*	0
Opana/Opana ER (oxymorphone) [76-41-5]	poorly absorbed; 50% excreted unchanged in urine	0
[d]OxyContin (oxycodone) [76-42-6]	4% excreted unchanged	271,636
[d]Percocet (oxycodone)		
[d]Reyataz (atazanavir) [198904-31-3]	7% unchanged in urine	14,000
Suboxone (buprenorphine/naloxone)	great variability in excretion of buprenorphine; mainly excreted in feces; conjugates excreted in urine	0
Subutex (buprenorphine) [52485-79-7]		0
Tequin (gatifloxacin) [112811-59-3]	70% unchanged in urine	12,500
Tyzeka (telbivudine) [3424-98-4]	extensively excreted unchanged	0
[d]Videx/Videx EC (didanosine) [69655-05-6]	extensively metabolized	0
[d]Xyrem (sodium oxybate) [502-85-2]	<5% excreted unchanged in urine	0
Zerit (stavudine) [3056-17-5]	16-62% unchanged in urine	2,120

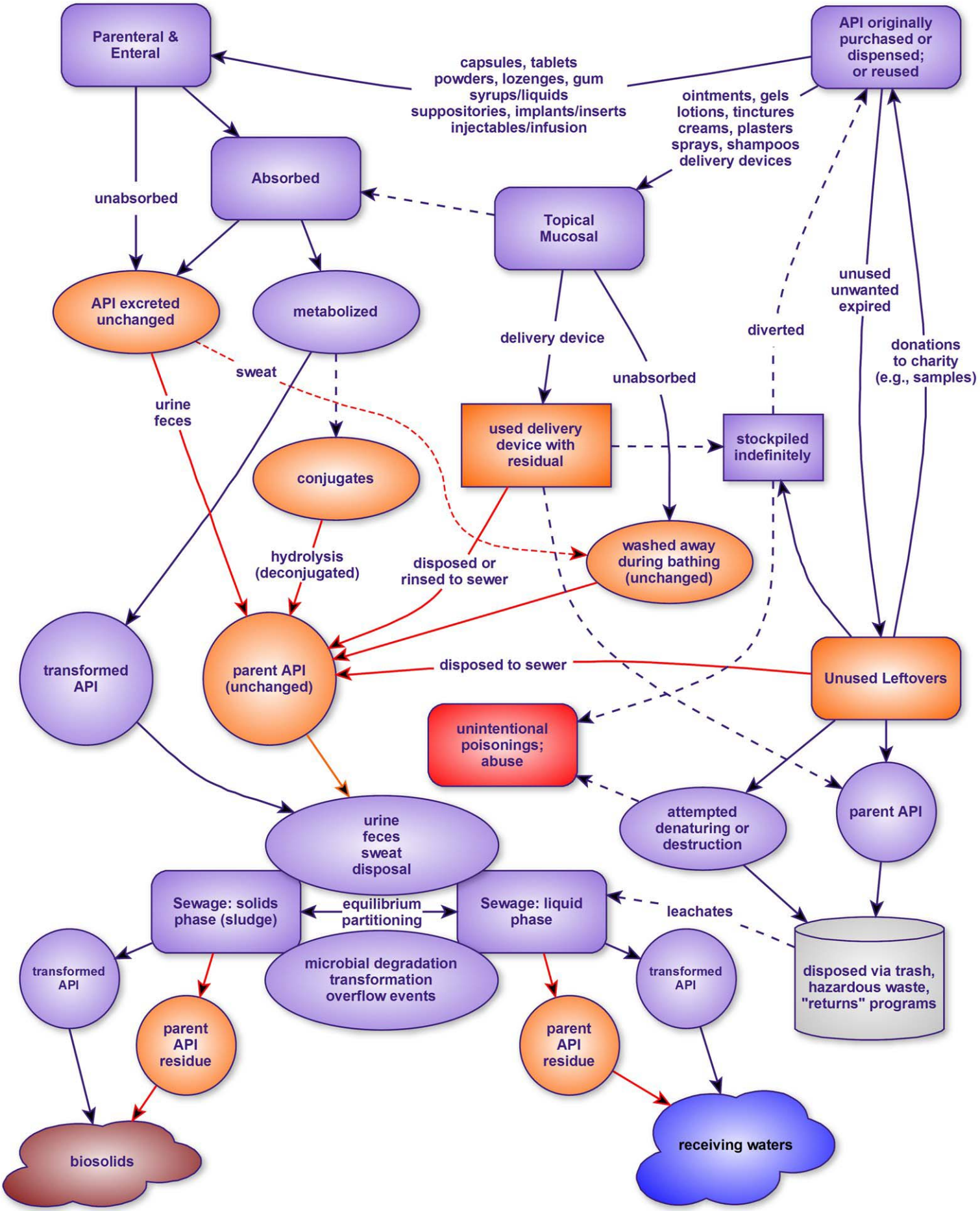
[a] Disposal by flushing recommended by OND.

([23] http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf) and/or manufacturers.)

[b] Note, however, that this assessment ignores the possible contributions from hydrolyzable conjugates or bioactive metabolites. Also note that elimination data for APIs is derived from testing on healthy humans. The actual percentage of clearance of unchanged API could be lower (but probably higher) in diseased patients or from those with certain metabolic polymorphisms.

[c] Data acquired from a single county (Clark County, NV, USA) over the course of 12 months [15].

[d] Drugs for which disposal may play a more dominant role in contributing to environmental residues; unless otherwise noted, pharmacokinetic data compiled from: ([152], http://www.rxlist.com; [153], http://www.druglib.com; [172], Physician's Desk Reference.2009. Medical Economics Data Production Company, Montvale, NJ, USA.


Parenteral & Enteral
capsules, tablets
powders, lozenges, gum
syrups/liquids
suppositories, implants/inserts
injectables/infusion
API originally purchased or dispensed; or reused
ointments, gels
lotions, tinctures
creams, plasters
sprays, shampoos
delivery devices
unabsorbed
Absorbed
Topical Mucosal
API excreted unchanged
metabolized
sweat
urine
feces
delivery device
unabsorbed
diverted
unused
unwanted
expired
donations to charity (e.g., samples)
used delivery device with residual
stockpiled indefinitely
conjugates
hydrolysis (deconjugated)
disposed or rinsed to sewer
washed away during bathing (unchanged)
transformed API
parent API (unchanged)
disposed to sewer
Unused Leftovers
unintentional poisonings; abuse
attempted denaturing or destruction
parent API
urine
feces
sweat
disposal
Sewage: solids phase (sludge)
equilibrium partitioning
Sewage: liquid phase
leachates
transformed API
microbial degradation
transformation
overflow events
transformed API
disposed via trash, hazardous waste, "returns" programs
parent API residue
parent API residue
biosolids
receiving waters